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A NEW AND ECONOMICAL DESICCATING PROCESS PARTICULARLY SUITABLE FOR THE PREPARATION OF CONCENTRATED PLASMA OR SERUM FOR INTRAVENOUS USE: THE ADTEVAC PROCESS *

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A PRACTICAL and inexpensive desiccation process is vital to the development of the widespread use of plasma and serum (ordinary or convalescent) because it solves two main problems in this field. First, storage difficulties practically cease to exist. While it is true that liquid serum may be stored, even without refrigeration as emphasized recently by Levinson,[1] there is no margin of safety. Contamination with but one bacterium could quickly spoil this excellent culture medium if stored without refrigeration. Also at room temperatures, the antibodies, prothrombin and other valuable biological properties rapidly deteriorate. By contrast, serum stored in the dry so-called lyophilic form will not support bacterial growth at any temperature, and in addition all the biological properties are preserved to a remarkable degree.

Under optimum conditions, no limit for the preservation of antibodies has yet been determined but it appears almost certain that immune sera can be preserved for many years. Even the highly labile complement has been successfully preserved by Kolmer [2] for 13 months. The possibility of almost indefinite preservation of potent convalescent sera, accomplished by an inexpensive method, brings the serum center and all its advantages within the scope of the average large hospital. With the necessity for rapid "turnover" of serum eliminated, such serum centers need not be limited to great centers of population as in the past. The safe, yet indefinitely long storage of whole plasma, possible in the dehydrated state, should also make practical

* Read at the annual meeting of the Texas Club of Internal Medicine, Dallas, February 16, 1940.

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the extensive use of the plasma treatment of shock in wartime. Being dry, the plasma could be contained in small metal ampoules or cans to facilitate shipment and handling.

The second problem solved by desiccation is the production of an ideal hypertonic solution for intravenous use, namely, concentrated plasma or serum. When the dried plasma is dissolved in distilled water any desired concentration from four times normal down to normal or even more dilute than normal (hypotonic) can be made as desired. This not only permits unusual flexibility, but also opens up new therapeutic possibilities in the regulation of fluid balance, blood volume and pressure, as yet only partially explored. Furthermore enough protein can be given as concentrated plasma with a large syringe (100 c.c.) at 12 to 48 hour intervals to sustain blood protein levels when food cannot be taken by mouth or when for other reasons protein levels are not maintained as in cirrhosis, cachectic states, etc.

These therapeutic advantages, peculiar to the intravenous use of human plasma or serum of various concentrations, have not as yet been generally appreciated. This has been due in a large measure to the limited supply of such plasma. Two reasons for this limitation have been apparent: first, the difficulty of obtaining a sufficient amount of blood, and second, the expense or complexity of available desiccating processes by which storage and concentration can be accomplished. Accordingly, it is the purpose of this paper to describe a new desiccating process employed at Baylor University Hospital for this particular use, and to report its routine operation in connection with a Blood Bank, to provide an adequate supply of plasma of any desired concentration up to four times normal.

In reviewing the development of desiccation of biological substances, it is of interest to note that definitely improved methods of desiccation have been followed by new and multiplied uses. On this basis two periods can be made out. In the first, desiccation was used on a very small scale for a limited amount of research and special teaching. In the second, research and teaching uses were expanded and desiccation was applied to preservation of convalescent sera in a few large centers. A third period, marked by the general preservation and use of whole plasma of various concentrations attained by means of desiccation, seems to be foreshadowed by the growing appreciation of the value of supporting blood protein levels, and of the use of concentrated plasma for its hypertonic effects.

Shakell [3] in 1909 discovered the basic principle of vacuum desiccation from the frozen state, which is so essential to the production of a highly soluble product with retention of its original properties. He also encountered the basic problem of this type of dehydration, namely, how to deal with the huge volume of water vapor released from only a few cubic centimeters of ice under the high vacuum conditions necessary to this process, a volume far too great for any pump to handle. Shakell solved this problem by chemical absorption and set a precedent followed by many investigators since. His choice of sulphuric acid for a desiccant as well as the design of his machine

definitely limited its use. Other workers using chemical absorption were Elser, Thomas and Steffen,[4] and Greaves and Adair [5] who improved machine design but found their methods severely restricted by the characteristics of the chemicals used. In general these difficulties were insufficient speed of absorption, dilution, scum formation, or other changes retarding the pickup of water vapor as the process proceeded. These difficulties increased with any increase in size of the apparatus. This, and the expense involved in using new desiccant each time, limited the use of these processes. In quality, however, satisfactory products were obtained. Elser, for example, was able to preserve cultures of meningococci and gonococci in viable condition for 18 years.

Greater possibilities in the field of desiccation were opened up when Elser introduced the use of very cold surfaces for the condensation of water vapor as ice. He first used CO_2 snow (— 70° C.) then mechanical refrigeration with resulting temperatures of — 34° C. These low temperatures were held in a refrigeration line within the manifold and resulted in a flow of water vapor from the frozen material being processed, to the refrigerator tubing where it was bound as super cold ice. This vapor flow was a result of the lower vapor pressure of the ice on the tubing in comparison to the vapor pressure of the ice in the ampoule. Elser also appears to have been first not only to employ manifolds with compression joint connections, but also to process large quantities of biologicals in original containers and to vacuum seal directly from the machine. Flosdorf and Mudd [6] employed similar principles in their machine, using dry ice in methyl cellusolve for the condenser refrigerant and effected an improvement by removing the cold surface from the manifold to a connected condenser chamber.

These improvements were followed by reports of clinical use of convalescent serum preserved and concentrated by the technic of Flosdorf and Mudd. McGuiness, Stokes, and Mudd [7] described good results in the use of convalescent sera preserved by desiccation. In a large series of cases results were found to be comparable with regular liquid serum, both in prophylaxis and treatment, but five fairly severe febrile reactions were observed. Stokes, Mudd, Arddy, Eagle, Flosdorf, and Lucchesi [8] made a similar report of the effective use of convalescent serum preserved by desiccation. Mudd, Flosdorf, Eagle, Stokes, and McGuiness [9] reported not only additional information on the keeping qualities and use of desiccated convalescent serum, but also detailed their technic of collections and filtration for intravenous use.

The value of the hypertonic qualities of concentrated serum was recognized in the experimental work of Bond and Wright [10] in the treatment of shock by its intravenous administration. Hughes, Mudd, and Strecker [11] reported the advantage of intravenous concentrated serum for the reduction of increased intracranial pressure. The effect of concentrated serum on the spinal fluid pressure was studied further in animals by Wright, Bond, and Hughes.[12] Aldrich, Stokes, Killingsworth, and McGuiness [13] used concentrated serum with good results to initiate diuresis in the treatment of

nephrosis. Ravdin [14] employed lyophil serum both concentrated and normal for the prevention and correction of hypoproteinemia after gastric operation. However, he hesitated to recommend it because of the frequency with which he encountered reactions.

The exact method of preparation of the serum used in the above reports was not always stated; presumably a low temperature condenser method was employed. At best, this method is too expensive for general use. A very much cheaper process, the Cryochem, was described by Flosdorf and Mudd [15] in 1938. They resorted to chemical absorption but with much greater success than earlier workers because of their choice of a much more suitable chemical, specially prepared anhydrous calcium sulphate, known as "Drierite." This process, although the most economical to date, still has serious drawbacks to be discussed later. A recent work on desiccation is that of Greaves and Adair.[16] They employ the older method of cold surface condensation of the water vapor but make important contributions to the study of the thermodynamics of desiccation. Bauer and Pickels [17] described a modification of the Flosdorf and Mudd Lyophil Machine in which they desiccated yellow fever virus. Continued frozen condition of the virus was assured by keeping it during processing in a hardening cabinet at — 18° C.

The Adtevac Process: Description of Principle and Operation

In attempting to build a machine at Baylor to operate with the Blood Bank, and suitable for the desiccation of large quantities of normal plasma as well as convalescent serum, we early realized the need, not for a different type of machine, but for an entirely new process. As a result, the older methods of cold surface condensation and chemical action were abandoned and experiments with a physical process, adsorption, were undertaken. The entirely new problems encountered in its use for this purpose were satisfactorily handled by the application of the principles of thermodynamics and proper engineering practice and design.

Like other processes, the one herein reported accomplishes desiccation from the frozen state by means of vacuum and removal of water vapor. The removal of water vapor, however, is accomplished in a manner entirely new in this field, namely by controlled adsorption. The operation can best be explained by reference to a simplified diagram of the machine, figure 1. The serum is contained in an ampoule (1) attached by a compression joint (2) and flexible metal bellows (3) to a vacuum tank (7) in which the adsorbent (8) is placed. When the vacuum pump (9) has sufficiently reduced the pressure in the system, rapid boiling occurs in the serum as dissolved gases, such as O_2, N_2, CO_2, etc., are released. During this phase the flexible metal bellows (3) permits lowering of the ampoule. The violence of the degassing process is controlled by admitting small amounts of air through a valve (4). This air is sterilized by passage through a suitable filter (5) and sterility maintained in the ampoule and manifold by properly locating a

valve so that the direction of flow is always away from sterile area to non-sterile. When degassing is sufficiently complete the valve (4) is kept closed and when the vacuum, as measured by a special gauge [12] goes to about 1500 (absolute pressure in microns) snap freezing occurs spontaneously as a re-

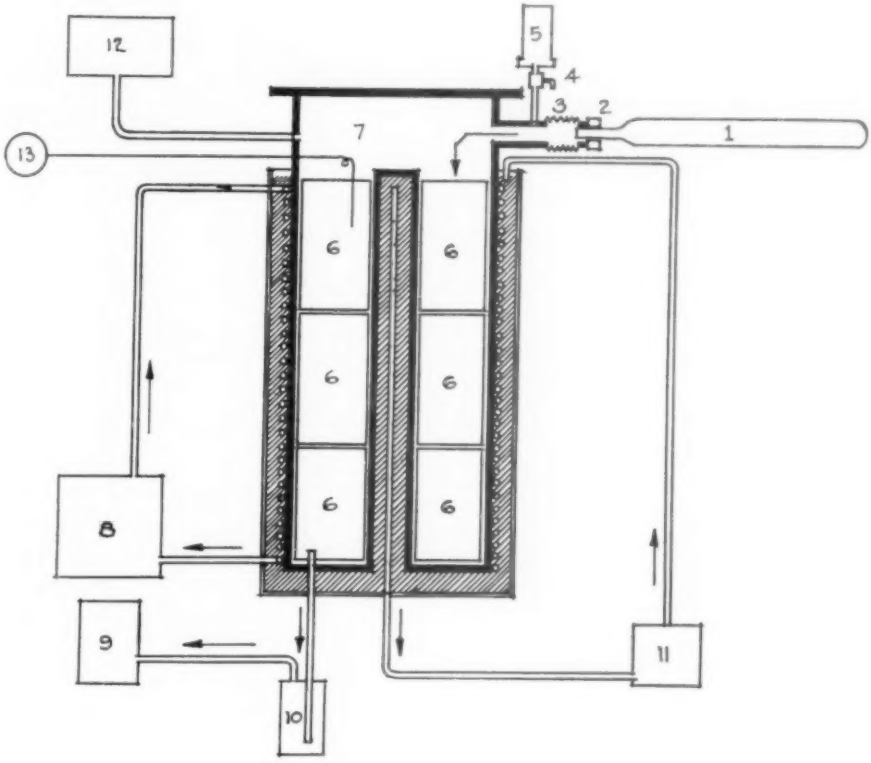

FIG. 1. Diagrammatic sketch of equipment.

sult of the rapid evaporation. Prior to freezing the ampoule is raised to a horizontal position to present a maximum evaporating surface. Evaporation (more correctly sublimation) continues from the frozen surface until the serum has reached the desired dryness.

In order to appreciate the advantages of controlled adsorption in our process it is necessary to understand the problem of water vapor removal. This apparently simple problem has presented most of the difficulties in all prior methods of desiccation.

In order to freeze and maintain the substance being processed in the frozen state, a sufficiently low vacuum must be held in the system. A vacuum pump is used to remove the non-condensible gases (air), from the system. Evaporation of water is accelerated as the pressure is reduced and in a relatively short time as the pump continues to remove the air, the system will be almost entirely filled with water vapor with continually diminishing

minimal quantities of air. When the point is reached where the air is eliminated and the system entirely filled with water vapor * a definite relation of temperature to pressure is found. This is according to the well known laws governing the pressure temperature relation of saturated steam or water vapor.

It is well known, for example, that the temperature in a steam sterilizer is related directly to the steam pressure and to the pressure only. Less familiar is the fact that the same relation in respect to water vapor holds as the pressure is reduced well below atmospheric levels. Below atmospheric levels the vacuum is conveniently expressed as absolute pressure in terms of the height of a column of mercury, as read by a special instrument. For example, at 9.1 mm. of mercury the temperature of saturated vapor is 10° C. This also means that at this pressure water boils at 10° C. At pressures below 4.5 mm. the temperature will be below the freezing point of water and under these conditions water in the system will have to be either in the form of ice or vapor.

This temperature pressure relationship explains why spontaneous freezing occurs in the ampoule when the absolute pressure falls below 4.5 mm. of mercury. It also indicates why the plasma remains frozen, with vaporization directly from the ice crystals continuing until dryness is attained. It is essential to note that once the water becomes vapor it must be regarded as a gas, subject to the laws of gases. As a consequence, we find that under the conditions of operation, for instance at an absolute pressure of 181 microns, the volume of water vapor resulting from the evaporation of one liter (one kilo) of water would be 4,670,930 liters. This indicates that no vacuum pump of reasonable size could remove the water vapor at sufficient speed. Failing to do this, the high vacuum necessary for the process obviously could never be attained, and freezing could not occur. Consequently, the necessity became apparent for some provision other than the vacuum pump, to remove the water vapor in the process.

In searching for a suitable substance to bind water vapor an adsorbent such as silica gel was suggested by two outstanding properties demonstrated by its use in the field of air conditioning. The first of these is its ability to take up very large quantities of water vapor up to 30 per cent in weight or more, and the second is the relative permanence of such substances. Since the union to water is physical, no appreciable deterioration occurs, upon drying off the water by heat, cooling and re-using. With reasonable care the adsorbent can be used indefinitely.

At this point a brief consideration of adsorption seems desirable. Adsorption is defined as the concentration of substances out of liquid or gaseous mixtures on the surfaces of liquids or solids. Many solid materials such as silica gel, charcoal, activated alumina, ferric hydroxide gel and others possess the power to adsorb gases and vapors to an unusual degree. According to

* Due to inevitable small leaks, a perfect saturated vapor condition is never actually attained. For practical purposes, however, it may be so considered.

Lednum [18] the mechanism by which this surface adsorption takes place is not actually known as the effects are beyond the powers of the most powerful microscope but a careful study by numerous investigators indicates the probable combination of three separate effects.

The first of these is probably the formation of a layer of the adsorbed

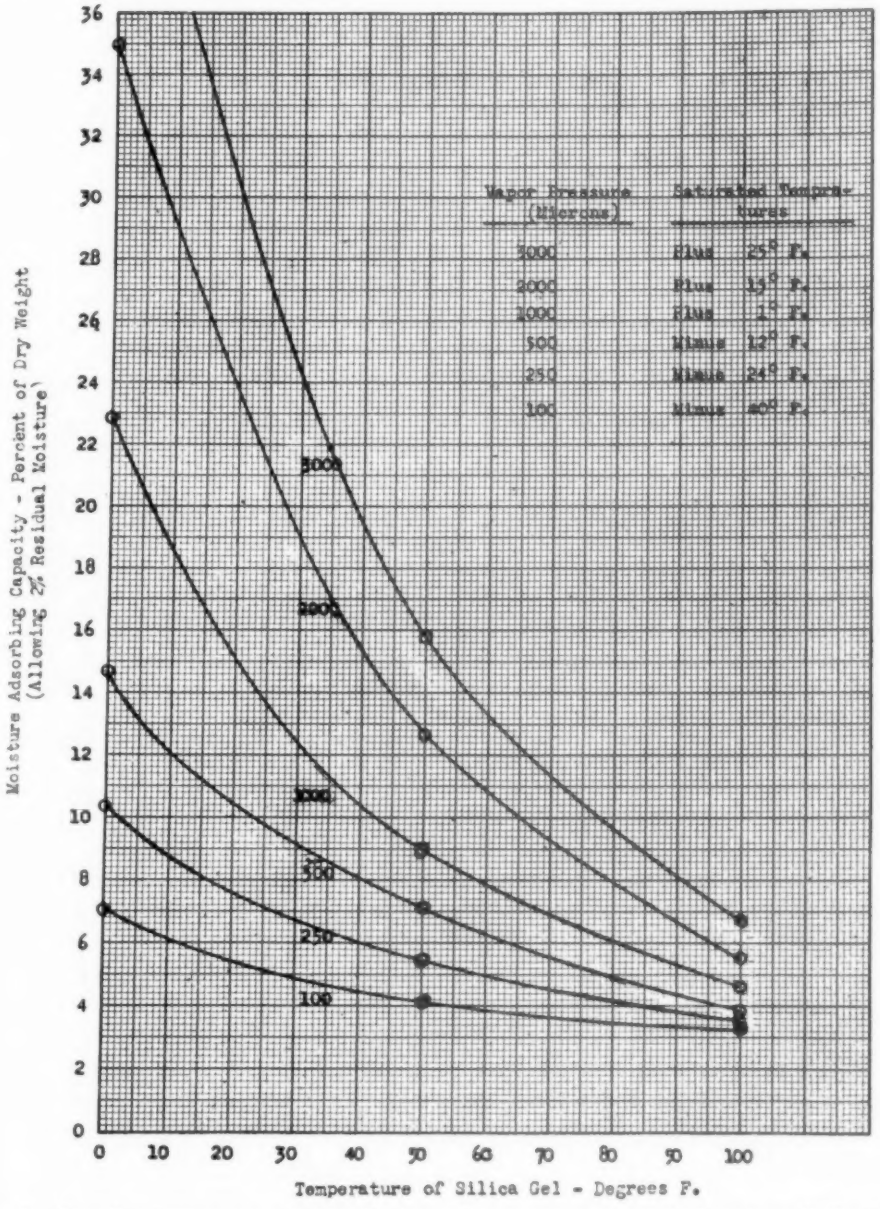

FIG. 2. Capacity-temperature relation of silica gel at vapor pressure (microns) as indicated on curves. Curve No. 2.

vapor one molecule deep on the surface of the solid. The second effect consists of the formation of a second layer of vapor of variable thickness held by the molecular attraction between the solid and the vapor, the thickness depending upon the strength of the attraction. The third effect is that of collection on the surface of submicroscopic capillary openings, of the more or less condensed layer of vapor. The three effects are cumulative, and adsorbing agents possess them in varying proportions to a greater or less degree. The amount of vapor adsorbed is, therefore, a function of the vapor pressure. It is evident that it must be also a function of the temperature. Change in either vapor pressure or temperature alters what may be called the " ease of condensation " of the vapor.

Reference to figure 2 shows that the capacity of a typical adsorbent (silica gel) to adsorb water vapor is dependent not only upon the vapor pressure to which the gel is exposed, but also upon the temperature of the gel itself. At low temperatures the capacity is greatly increased, while rising temperatures in the adsorbent are accompanied by diminished capacity to take up water vapor. This fact is of great practical importance since a definite amount of heat is liberated when the adsorbent takes up water called the heat of adsorption, which by raising the temperature of the adsorbent tends to reduce its capacity for further binding of water. In our machine this heat is removed by a small standard refrigeration unit. The actual transfer of heat can easily be accomplished in several ways according to the engineering design, by providing suitable metal pathways.

By this arrangement of refrigeration and heat transfer it is not only possible to remove the heat generated during the operation of the process, but it is also possible to cool the adsorbent and improve its effective capacity. Furthermore, since the greatest flow of vapor occurs early in the process, just prior to freezing, with consequent generation of unusual amounts of heat, it is best to pre-cool the adsorbent to accommodate this temporary heavy load.

If desired the plasma may be pre-frozen in the ampoules. This of course is desirable when desiccating small amounts such as are employed in storing complement, cultures, and in other laboratory uses.

As Greaves and Adair [16] have pointed out, the desiccation time can be greatly shortened by applying heat to the substance being processed, especially in the earlier stages. This heat is translated into an increased flow of vapor from the frozen surface, but if this increased flow can be removed rapidly by the desiccant the pressure in the ampoule need not rise significantly and as a consequence the temperature will be substantially unchanged. In the Adtevac process advantage can be taken of this fact due to its ability to take up large volumes of water vapor rapidly. This represents a definite advance in speed of processing since earlier methods were easily overloaded when acceleration of evaporation by heat was attempted, as Greaves and Adair [16] showed.

For the desiccation of large quantities of ordinary plasma we have used ampoules of great capacity, usually 500 c.c. We have not observed the restrictions laid down by Flosdorf and Mudd [6] in respect to ratio of fluid volume to surface. On freezing, stratification occurs with great increase of surface with satisfactory rapid drying. The size of the ampoule neck has been kept as large as possible to keep restriction of vapor flow to a minimum. The use of metal bellows for flexible coupling has also eliminated the constriction which rubber tubing always imposes. With 200 c.c. quantities per ampoule satisfactory drying of plasma has been accomplished in six hours.

Figure 3 is a photograph of the machine now in use.

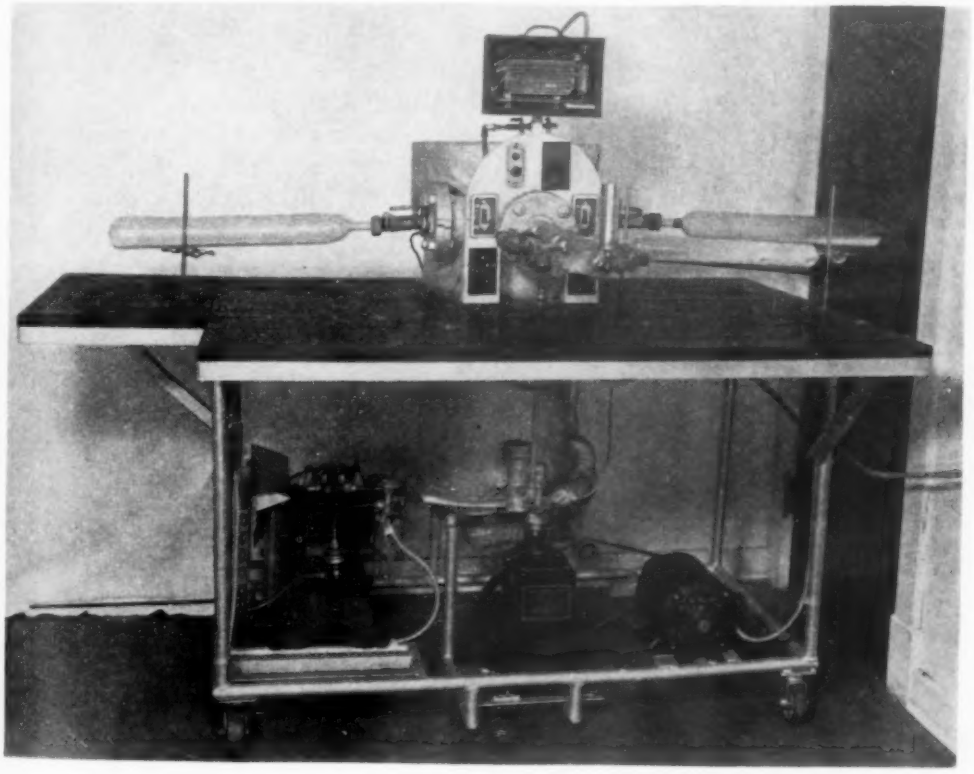

FIG. 3.

DISCUSSION

In comparing our process with prior methods we have considered the following points: quality of product, economy of operation, practical maximum capacity, reliability, ease of operation, and initial cost.

The quality of materials can be estimated most satisfactorily by extensive use. Our clinical results from the intravenous administration of plasma desiccated by this process are briefly summarized in a later section of this

paper. Another test of quality, however, is the determination of residual dryness according to the method of Flosdorf and Webster. They state that a residual moisture of 1 per cent or less is satisfactory for biological use. We have found that the possible dryness obtained varied with the moisture load imposed on the adsorbent. However, even with maximum loads it was found possible to attain moisture analyses of less than 1 per cent. However, when plasma was further subjected to desiccation with a new dry charge of adsorbent substituted for the already used, thus operating the process in two stages,* the residual moisture is almost too small for accurate analysis. For example, under these conditions moistures of .03 per cent and less are obtained.

The chief advantage of the new process is the economy of operation. Unlike earlier methods using chemical absorption, the Adtevac process does not require the frequent replacement of expensive desiccants. Furthermore, much larger quantities of water for a given weight of adsorbent can be taken up at one operation. This emphasizes the disadvantages of chemical union with water vapor as contrasted with adsorption, since by our method as high as 14 per cent capacity has already been realized. Theoretical considerations indicate a considerably higher capacity can be attained under optimum conditions.

The limited space usually allotted to hospital laboratories makes it desirable to have a maximum capacity for unit size. In this respect the new adsorption process enjoys a marked advantage due to the high capacity per unit weight.

The actual process has proved itself reliable and easy to operate over a period of many months. It should be noted that the refrigeration unit employed in this machine is a small commercial unit operating under ordinary temperatures and is not to be confused with the huge refrigeration system employed in the direct cold surface condensation methods where operation must be conducted in the difficult sub-zero region.

Experiments now in progress indicate another advantage of controlled adsorption for desiccation. The great capacity to take up water vapor rapidly, permits the application of relatively large quantities of heat to the ampoules without melting the contained material. This drives off the vapor more rapidly and greatly shortens the desiccation time. Also important is the margin of safety that this capacity gives under normal operating conditions when substances such as virus preparations are to be desiccated, since evaporation will continue with such speed that the temperature will remain well below freezing until the desiccation is essentially complete.

This is a point of greatest importance, if overloading and thawing or even near thawing is to be avoided. Proper attention to these considerations

* Note: For large capacity machines this two-stage operation can be used routinely, by employing two desiccant chambers. These are both connected to the manifold by electrically operated remote control valves contained within the large tube uniting the two chambers. Such a valve presents no difficulty because of the slight difference in absolute pressure in the two chambers.

would probably eliminate the need for cumbersome and expensive external refrigeration of the containers or ampoules.

Estimates of the initial cost of the machine are not as yet complete, but it is apparent that on a capacity basis it should be considerably less than machines now available.

Source of Plasma Supply

The Blood Bank constitutes an ideal organization to obtain an adequate supply of plasma. Donors are required to give an amount of blood sufficient to produce the amount of plasma given. For example since blood is about one-half plasma and since a four times concentration is effected, it would theoretically require eight times the volume of blood to produce the maximum concentration of serum. Since some plasma is lost in separation from cells, and in filtration, a 10 to 1 ratio is more nearly correct.

Blood given for the purpose of replacing plasma is ordinarily kept in the Blood Bank up to the maximum of 10 days. This is of value to the Blood Bank in keeping an adequate supply of all types of whole blood available. Conversely, the Blood Bank is of assistance to the plasma department since all blood from the bank when outdated at the tenth day is processed and stored.

In preparing the plasma a technic similar to that of Mudd, Flosdorf, Eagle, Stokes and McGuiness [9] was used at first. More recently a new technic, eliminating the restrictions imposed by the type specific agglutinins has been adopted as routine. The removal of agglutinins is accomplished by adsorption on red cells as a result of pooling the different types of whole blood and immediately separating the plasma.

Accompanying hemolysis is kept at a minimum by working rapidly at low temperature. Hemolysis is also retarded by the low complement content of 10 day old blood. However, some hemolysis has occurred with definite coloring of the plasma. An approximate determination by the Newcomer method using a one to four dilution has shown a maximum of 0.3 grams per 100 c.c. of plasma. The agglutinin titer has varied from 0 to 1 : 1.

Since we have observed no evidence whatever that hemolysis causes reactions in six months' experience with blood banking we did not hesitate to use plasma containing small amounts of hemoglobin. This is contrary to the commonly accepted opinion in blood banking. However, no febrile or other type of reaction (with the exception of two transient urticarial manifestations) has been observed in the use of such plasma in concentrated form.

Following a suggestion of Levinson,[19] we have omitted filtration of plasma after desiccation and reconstitution as a liquid. Clinical results have been unchanged, and loss of valuable concentrated plasma in the filter is thus eliminated. Seitz filtration of plasma separated from pooled blood is performed prior to processing.

Plasma intended for long storage is vacuum sealed in the original am-

poules. For current routine use, the plasma is redissolved in pyrogen free water to make a four times concentration, placed in small Erlenmeyer flasks, and kept frozen at — 18° C. For use this plasma is melted in a 37.5° C. water bath and given with a large syringe (100 c.c.).

Indications and Clinical Results

The plasma has been given in concentrated form (1) to replenish deficiencies in blood protein, (2) to build up or sustain blood volume, (3) for hypertonic effect in reducing edema, and (4) in a miscellaneous group. When hypertonic effects were not desired or if additional fluid was needed, a suitable amount of saline was given after the administration of the concentrated plasma.

To date 66 doses of concentrated plasma have been given intravenously to 45 individuals. In this series no definite febrile reactions were encountered in any instance. In fact, examination of charts of these patients shows that febrile patients have as a rule exhibited a substantial drop in temperature of 1 to 1½° F. depending somewhat upon the height of the fever. As a rule the plasma was given over a period of 10 to 15 minutes, but on some occasions, particularly in emergency, such as in severe shock, the entire dose has been given as quickly as 1½ minutes. The largest dose given at one time was 170 c.c. This would be equivalent in protein content to 1360 c.c. of whole blood. This is in accord with the practice of not exceeding 200 c.c. for a single dose to adults.

A detailed analysis of clinical results will be reported later when a larger, more complete series of cases has been compiled. However, even in this small series fairly obvious and definite advantages in the use of concentrated whole plasma stand out. The best results were obtained where there was local edema combined with reduced blood volume in shock. This was to be expected since concentrated plasma builds up blood volume by withdrawing water from the tissues. Such cases as shock with head injuries have responded favorably.

In shock from acute hemorrhage (ruptured ectopic pregnancy) concentrated plasma has rapidly built up the blood pressure prior to transfusion and operation.

In a small series of burns, several very severe cases have responded to the use of concentrated plasma with the relief of shock and apparently accelerated healing with maintenance of blood protein levels. The plasma was given with or without additional fluid according to the patient's fluid balance. Concentrated plasma alone was employed to advantage when the patient was "water logged" from prior administration of large amounts of saline.

Blood protein levels have been successfully maintained by the intravenous administration of concentrated plasma in several cases where adequate diet could not be taken by mouth. These patients all showed improvement with increase in strength.

Convalescent sera have also been dried, stored and used with good results. Obviously time has not permitted the determination of the effect of prolonged storage.

The process has been entirely satisfactory for laboratory uses such as preservation and concentration of typing sera, preservation of cultures, positive sera, and thromboplastin extracts for the prothrombin test.

Conclusions

1. A new and improved process for the desiccation of plasma, serum and biological substances from the frozen state is reported.
2. The thermodynamics of this type of desiccation are investigated and discussed.
3. The operation of this process in connection with a Blood Bank to assure an adequate supply of plasma for routine intravenous use is described.
4. A preliminary report of clinical results in a variety of conditions is given.
5. No febrile or other harmful reactions were noted in 66 successive intravenous administrations of concentrated plasma to 45 cases.

BIBLIOGRAPHY

1. Levinson, S. O., Neuwelt, F., and Nechelese, H.: Human serum as a blood substitute in the treatment of hemorrhage and shock, Jr. Am. Med. Assoc., 1940, cxiv, 455–461.
2. Kolmer, J. A., Richter, C. E., and Lynch, E. R.: Lyophile complement fixation test for syphilis, Am. Jr. Clin. Path., 1938, viii, 522–528.
3. Shakell, F. F.: An improved method of desiccation with some applications to biological problems, Am. Jr. Physiol., 1909, xxiv, 325–340.
4. Elser, W. J., Thomas, B. A., and Steffen, G. I.: Desiccation of sera and other biological products (including microörganisms) in the frozen state with preservation of original qualities of products so treated, Jr. Immunol., 1935, xxviii, 433–473.
5. Greaves, R. I. N., and Adair, M. E.: Simple method for the preservation of sera by desiccation in frozen state without use of refrigerants, Jr. Hyg., 1936, xxxvi, 507–513.
6. Flosdorf, E. W., and Mudd, S.: Procedure and apparatus for preservation in "lyophile" form of serum and other biological substances, Jr. Immunol., 1935, xxix, 389–425.
7. McGuiness, A. C., Stokes, J., Jr., and Mudd, S.: Clinical uses of the human serums preserved by lyophil process, Jr. Clin. Invest., 1937, xvi, 185–196.
8. Stokes, J., Mudd, S., Arddy, R. L., Eagle, Harry, Flosdorf, E. W., and Lucchesi, P.: Use of lyophile human serums for prevention and treatment in infectious diseases, Am. Jr. Dis. Child., 1934, xlviii, 1428–1430.
9. Mudd, S., Flosdorf, E. W., Eagle, H., Stokes, J., and McGuiness, A. C.: Preservation and concentration of human serums for clinical use, Jr. Am. Med. Assoc., 1936, cvii, 956–959.
10. Bond, D. D., and Wright, D. G.: Treatment of hemorrhage and traumatic shock by the intravenous use of lyophile serum, Ann. Surg., 1938, cvii, 500–510.
11. Hughes, J., Mudd, S., and Strecker, E. A.: Reduction of increased intracranial pressure by concentrated solutions of human lyophile serum, Arch. Neurol. and Psychiat., 1938, xxxix, 1277–1287.
12. Wright, D. G., Bond, D. D., and Hughes, J.: Reduction of cerebrospinal fluid pressure by concentrated lyophile serum; further observations, Arch. Neurol. and Psychiat., 1938, xxxix, 1288–1293.

13. Aldrich, C. A., Stokes, J., Jr., Killingsworth, W. P., and McGuiness, A. C.: Concentrated human blood serum as diuretic in treatment of nephrosis; preliminary report Jr. Am. Med. Assoc., 1938, cxi, 129–133.
14. Ravdin, I. S.: Some recent advances in surgical therapeusis, Ann. Surg., 1939, cix, 321–333.
15. Flosdorf, E. W., and Mudd, S.: Improved procedure and apparatus for preservation of sera, microörganisms and other substances—cryochem-process, Jr. Immunol., 1938, xxxiv, 469–490.
16. Greaves, R. I. N., and Adair, M. E.: High-vacuum condensation drying of proteins from frozen state, Jr. Hyg., 1939, xxxix, 413–445.
17. Bauer, J. H., and Pickels, E. G.: Apparatus for freezing and drying virus in large quantities under uniform conditions, Jr. Exper. Med., 1940, lxxi, 83–88.
18. Lednum, J. M.: Theory of adsorption. Read before Industrial Gas Section, sixteenth annual convention and exhibition of Am. Gas Assoc., Atlantic City, N. J., (Oct. 30), 1934.
19. Levinson, S. O.: Personal communication.

RUST AND SMUT, MAJOR CAUSES OF RESPIRATORY ALLERGY *

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DURING the past few years we have observed that a certain number of patients manifested unusually severe asthmatic symptoms during the month of July and during the early part of August. We attributed this at first to such pollens as the plantains and lambsquarter, and to a residual effect of the timothy pollen. However, by thoroughly checking the symptoms against the daily pollen counts, by frequently retesting for the then prevailing pollens, and by administering what we felt was adequate treatment to those patients who exhibited more or less pronounced reactions to these pollens, we were unable to establish such an etiological correlation.

Another source of asthma during that period was suggested by the studies of Feinberg [1] on molds. In pursuance of his work we carried out a local survey during the past year in collaboration with Ackley.[2] The data obtained from this survey warrant the conclusion that those fungi which Feinberg named as the most probable causes of asthma, namely alternaria and hormodendrum, did not play the major rôle in causing the symptoms in our patients. The following evidence shows, instead that spores of smut and rust in the air were instrumental in causing allergic symptoms of the respiratory tract during that period of time.

The literature includes three cases of asthma reported by Cadham [3] in 1924 in which wheat rust was believed to be the cause. In his report, however, Cadham presents definite confirmation of the clinical impression by skin tests. Another more recent paper by Wittich and Stackman [4] relates the case of an individual working in a milling district whose asthma was caused by corn smut. This paper is illustrated by a photomicrograph of smut present in the stained sputum. Wittich [5] has recently observed 11 asthmatic patients in whom smut sensitivity appeared to be the major cause. Duke and Durham [6] were first to mention the appearance of rust and smut spores on exposed slides. They found that in Kansas City during May, June, and July, 1927, rust spores were more numerous than all other types of pollen grains. Durham [7] noted in his recent survey on fungi that spores of smut and rust appear very frequently. Brown [8] considered grain rust (*Puccinia graminis*) of sufficient importance to include it in his routine skin testing for molds.

In an investigation of this subject, one of the chief difficulties encount-

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ered in the preparation of a pure extract is that smut does not grow readily on artificial media, and that the culturing of rust is impossible.

A brief description of the mode of occurrence of rust and smut in nature is necessary in order to understand its effect on asthma.

Smut

Smut fungi occur on a wide range of hosts, the most common ones being the cereals and grasses. In this part of the country the most important species are the stinking smuts of wheat (*Tilletia tritici* and *levis*), the smut of corn (*Ustilago zeae*), and that of oat (*Ustilago levis*). Smut spores infest the plant of the grain by attacking its fruit where they develop black, dusty masses. In some grains, for instance in corn, they produce tumor-like formations of considerable size which usually replace the tassels and the ear of corn in its entirety. When the fungus has used up all the tissue of the affected organ as food material, the whole diseased structure represents a mass of hyphae which produce millions of black spores called chlamydospores. At harvesting time these spores separate from the hyphae, are scattered by the wind for many miles, and settle upon old corn stalks, soil, or manure, where germination takes place the following spring. A large part of the spores may remain alive for four to five years, especially under the influence of moisture. When the new spores begin to bud they produce another type of spores called basidiospores. These are readily carried by the wind when the seed germinates, and infest the young seedlings of grain. They grow up with the stem of the grain and attack the young kernels by feeding upon their substance.

The smut spores which we observed on our slides in midsummer are the chlamydospores. They are round, brownish-black bodies, variously sculptured, showing small spicules on their surface similar to those of ragweed pollen. Most smut spores are considerably smaller in size than ragweed pollen, having a diameter of 5 to 9 microns. Some smuts are difficult to cultivate even if the grain of their host is used as culture material. The spreading of the spores and the breaking up of smut balls are greatly aided by the threshing of the grain. During this time the air becomes more intensely filled with the spores.

Rust

The growth of rusts is more complex than that of smuts since rust requires two hosts for the completion of its life cycle. Rust spores infest the stems, not the fruit, of the various grains, grasses, and fruit trees. We have been particularly concerned with grain rusts (*Puccinia graminis*), especially those of wheat and barley. We are also studying rusts of grasses, especially of timothy and blue grass.

The spring stages of the wheat rust occur upon the leaves of the common barberry bush, the summer and winter stages on the stems of the wheat plant.

Barberry Stage: In early spring two types of "yellow pustules" appear on the barberry leaves. They can first be seen on the upper surface; and shortly after larger sized pustules appear on the lower surface. These pustules are made up of numerous small, cup-like structures called aecia. When these cups break open they discharge masses of yellow spores called aeciospores, which are scattered by the wind.

Grain Stage: The aeciospores fall upon the young stems of grains, produce elongated yellow streaks underneath the epidermis of the stems and the leaf sheaths of the grain. This first visible evidence of rust on cereals is called uredinia or red rust. With further growth the lesions push outward and finally break through the surface, thus exposing a reddish brown mass of spores (urediniospores). They are stalked, one-celled, and ovate in form. Each spore contains two nuclei, is rather thick-walled, and bears numerous small, spiny projections. Under the influence of moist, warm weather they may produce successive growths of their own kind about every seven to 10 days throughout the growing season. These spores are disseminated by the wind; they were found on our slides throughout June and July. Durham states that in large grain centers of the United States, the concentration of wheat rust in the air may reach 980,000 spores per cubic yard.

Usually in late summer and fall, black pustules or telia, containing teliospores, appear on the same culm and leaves. These pustules are dark-colored, stalked, bicellular, with a diploid nucleus, spindle-shaped, and thick-walled. Unlike its predecessor, however, the teliospore cannot germinate immediately, but must pass through a dormant period, wintering on the stubble or on the ground until early spring. Then the black pustules send out small, thin-walled, short-lived spores called basidia which are carried by the wind to the barberry leaves. There they start the life cycle anew.

Spore Count

Since July, 1938, we have charted the number of rust and smut spores found on the vaseline-coated slides which were exposed for 24-hour periods for our routine pollen counts. Figure 1 presents the daily number of the rust and smut spores counted on 1.8 square centimeters of the exposed slides. This curve is compared with that of alternaria, which is the most easily recognizable fungus spore in season at that time, and with the curve of the two most important pollens then encountered, namely timothy and ragweed. Because of the difficulty in differentiating definitely between the rust and smut spores on the slides, we did not attempt to present separate curves for each. The first urediniospores of rust occurred about July 15 and reached a rather high peak about July 21, on which day 149 spores were counted. The peak on July 30 is probably attributable chiefly to smut, but there was still a small number of rust spores on the slides during the early part of August. In comparing this curve with those of timothy and ragweed pollen, and that of alternaria spores, we find that the peaks of the rust and smut curve are higher

than that of timothy, but not as high as that of the ragweed curve. Alternaria was present throughout the time of observation and continued late into the fall. Other investigators have stressed the importance of alternaria as a cause of seasonal asthma, particularly in July and August. The alternaria curve shows a more or less generalized distribution of the spores throughout the whole time of observation with relatively little variation and only a few discernible peaks.[2] In our experience with pollen [3] we noted that

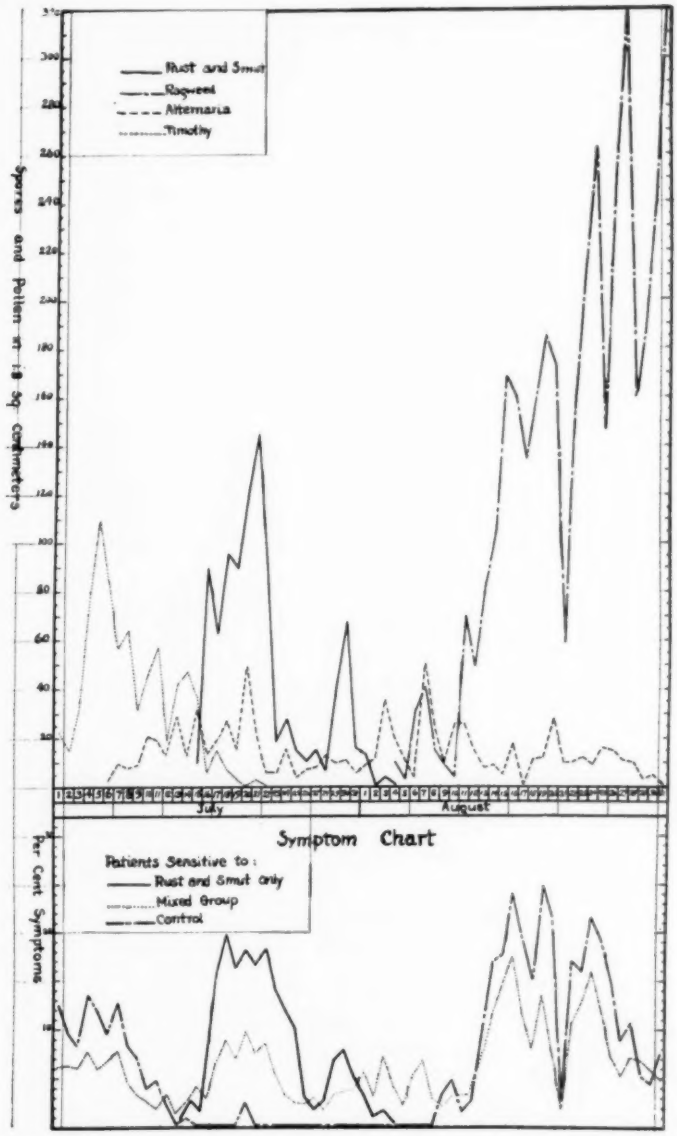

FIG. 1. Daily rust and smut count compared with counts of ragweed, timothy, and alternaria. The symptoms chart below shows the summation of the daily "symptom marks" for each group of patients.

the severity of symptoms of hayfever and asthma does not depend as much on the quantity of a certain pollen in the air as on the rapidity of the increase and decrease in its concentration. If this observation can be accepted in the interpretation of the fungus spore curve, we would expect to encounter more symptoms from sensitization to rust and smut than to alternaria because of the different character of the curves.

Method

Our clinical observations are concerned with the summer stage of rust, namely the urediniospores, and the chlamydospores of smut which were present on our slides at the time in question. Extracts were prepared from the pustules of red rust of wheat and oats and the smuts of oats, barley, and corn. The mechanically separated fungus material was killed by exposure to 5 per cent thymol in concentrated alcohol. This was evaporated, and the residue was extracted in saline solution and passed through a Seitz filter.

Our survey was carried out on 106 consecutive patients with asthma and nasal allergy. Among these, seven asthmatics exhibited symptoms at no other time than late July and early August. In a second group of 12 patients, 10 suffered more or less severe exacerbations of a perennial asthma during that time, and two suffered similar exacerbations of nasal catarrh. The other 87 cases exhibited no symptoms at the time in question.

The adequacy of this arbitrary division of our cases into three groups was well illustrated by a study which had been carried out for another purpose. Throughout the summer months of 1938 most of our patients had been instructed to keep a very close record of the dates of their symptoms. In their daily symptom chart the severity was graded one to four plus. We were able to utilize the records of all the patients of groups one and two, and 48 of those of group three. The second portion of figure 1, marked "symptom chart," represents a summation of the plus marks on these records. A definite parallelism of the "symptom curves" with the fungus curves is noticeable in the first and second groups, a fact which is highly suggestive of an etiological connection of the symptoms of these patients with the rust and smut.

Scratch and intradermal skin tests were performed for the rusts of wheat and the smuts of corn and oats. As control tests we applied extracts from the grains, as well as of the straws of the selected rusts and smuts, namely of wheat, oats, and corn. Furthermore, we tested all of the 106 patients for alternaria, hormodendrum, and penicillium, as well as for timothy and ragweed, since these pollen and fungi were constantly present in the air during the season in question. The straws of wheat, corn, and oats which were used for extraction had been examined microscopically and were found to be free of rust and smut infection. We felt that this latter control was indi-

cated because of the possibility that, with our mode of preparation of the rust, skin reactions to straw could have been encountered.

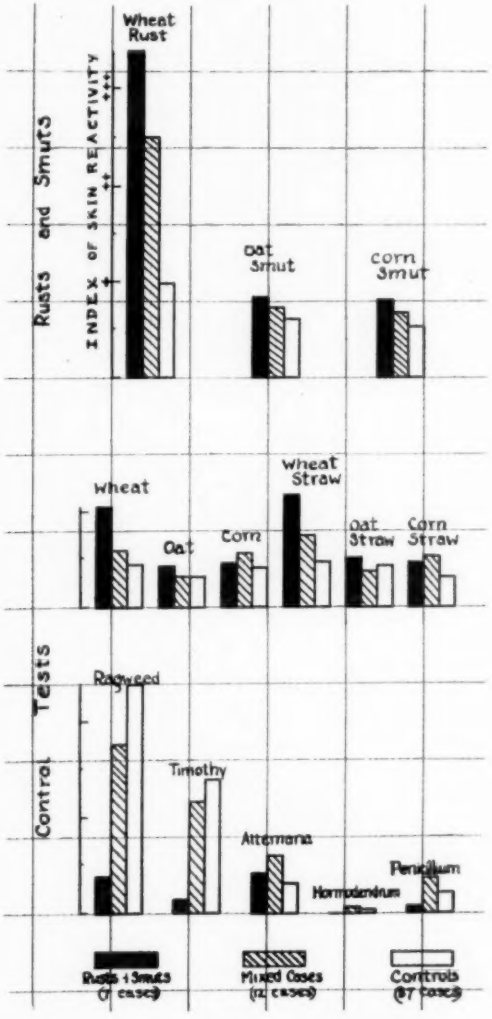

FIG. 2. Average size of skin reactions for wheat smuts, oat and corn rusts in the three groups of patients, compared with the skin reactions of the control antigens.

RESULTS

Figure 2 records the averages of the intradermal skin reactions which had been graded from one to four plus in the three groups of cases under consideration, namely, in those patients who had symptoms exclusively during the rust and smut season (seven), those who suffered definite exacerbations at the time (12), and the control group of 87 cases without manifestations at the season in question.

The three groups, which were arbitrarily established by the history of their symptoms, showed also a distinctly different response to skin testing which conformed well with our clinical impression. The seven patients with symptoms only in July and early August exhibited by far the strongest reactions to the rust and smuts, whereas their reactions to pollen and the other fungi were considerably less pronounced. The 12 patients suffering exacerbations at the rust and smut season reacted less to rust and smut, but gave stronger reactions to the pollens and the other fungi. In the control group the reactions to rust and smut were negligible, but those to pollens were most pronounced. The smut and rust sensitive patients were also more sensitive to the respective cereals and their straws than were the other patients. In no case, however, was the individual reaction to the grain as strong as that to the fungus.

The total group of patients gave only minor skin reactions to the other fungi tested, such as penicillium and hormodendrum. This may or may not indicate a relative lack of significance of these molds in a consecutive number of allergic patients in this part of the country as compared with rust and smuts.

Clinical Observations

During this study we encountered two patients in whom the intradermal skin tests for rusts produced generalized reactions, even though the usual precautions of a preliminary scratch test were carried out. Hyposensitization with rust and smut extracts was attempted in all of the suspected cases. In some the effect was very striking, the symptoms subsiding after two or three injections. The evaluation of the effect of this treatment, however, is difficult because of the relatively short duration of the fungus season, which may have accounted for spontaneous recovery in some of the patients.

There are many different types of rusts and smuts as pointed out above. Unfortunately, we were unable to carry out extensive cross testing with the various species. The majority of the patients with positive reactions to rusts also reacted positively to smuts, but the reactions to smut were not as frequent and as pronounced as those to rust. The serum of two patients with strongly positive intradermal responses to rust produced positive passive transfer reactions on normal individuals. The following two cases, namely, patients who had symptoms at this season only, and those who suffered aggravation of symptoms during the season in question, are reported because they are typical of the two first groups. In both cases asthmatic symptoms were reproduced upon inhalation of rust powder outside of the season.

Case Reports

Case 1. R. D. C., a 20 year old male, consulted us on March 7, 1938, because of symptoms of "hay-fever" and a severe cough, which had occurred during July and August for the past three years. During the balance of the year, and especially during the ragweed season, the patient stated that he had been free from symptoms.

There was a positive familial history of allergy. The patient has had no other symptoms of allergy with the exception of "chronic sinusitis" about eight years ago which was promptly remedied upon removal of several polyps. He had had the usual childhood diseases, and pneumonia in 1935 and 1938.

The physical examination revealed nothing unusual, particularly with reference to the nasal passages and sinuses. Intradermal skin tests showed largely negative reactions, with exception of the tests to a few foods and to short and long ragweed and cocklebur. The latter reactions were two and three plus. Not having any other clue for treatment at the time, we gave the patient weekly injections for these pollens. About July 5 the nose became markedly congested, and within the following days a typical state of asthma developed which was particularly pronounced at night.

On July 8 intradermal tests for fungi, following scratch tests, revealed four plus reactions to rust, two plus reactions to smut, and a two plus reaction to monilia. Within 10 minutes after the injections a generalized reaction occurred which appeared to have its origin at the site of the rust injection. This was promptly controlled by 0.2 c.c. of epinephrin. The asthmatic condition, as well as the nasal symptoms, subsided promptly for about three days. During the following days treatment with a 1 : 100,000 dilution of rust extract was given which completely relieved the patient. On December 18 a small amount of rust powder was blown into the air close to the patient's nose. A violent attack of sneezing, followed by asthmatic wheezing, was precipitated within a few minutes. Administration of 0.5 c.c. of epinephrin promptly controlled the attack.

Case 2. F. K., a four year old boy, was first seen on July 11, 1937, because of asthma which had been present practically throughout the year for two consecutive years, with definite aggravations about July and August. He also presented evidence of pronounced allergic eczema on hands, face, and neck, which had first appeared when he was six months old. Various members in both parental families were reported to be allergic. When the patient was first seen the symptoms of rather severe asthma were present and a large number of positive skin reactions was obtained, particularly to wheat, milk, egg, several trees, and grasses. An eliminative régime, as well as hyposensitization against the most important reactors, resulted in improvement of the eczema. The asthma, however, did not subside until the first part of September. During the winter months of 1937–1938 the boy was entirely free from asthma and suffered only from occasional upper respiratory catarrhs.

In March 1938 retesting with most of the previously reacting antigens showed no essential change. The test for wheat rust and corn smut was four plus, and that of oat rust, two plus. Among other fungi, hormodendrum, penicillium, and monilia gave one to two plus reactions. Hyposensitization with 26 injections of wheat rust extract was initiated with a 1 : 1000 dilution, which resulted in very strong local reactions at the site of injection. During 1938 only one asthmatic attack occurred, on July 18, which we felt was due to the combined effect of the rust spores in the air and a rather large dose of the rust extract administered that day. Otherwise the boy has been entirely free from trouble. On January 6, 1939, the boy was subjected to inhalation of dried alternaria powder which caused no irritation whatsoever. When the powder of rust was blown toward his nose violent sneezing, followed by some wheezing, ensued, from which the boy recovered spontaneously within 15 minutes.

Comment

It is true that in a given case it is often difficult to evaluate the importance of a certain antigen as the cause of allergic manifestations on the basis of clinical evidence. However, when the cases are as numerous as those re-

corded here we feel justified in assuming that rust and smut play a prominent part as a source of asthma and upper respiratory allergy. The following reasons emphasize this point:

1. The spores of rust and smut are small in size and spiculated, making them more buoyant. In contact with respiratory mucous membranes they are likely to produce more irritation than antigens with a smooth surface.

2. The mode of appearance of the spores in the air, as indicated by the spore curve, is particularly apt to induce symptoms. Their periodic appearance in midsummer, their absence during a large part of the year, the relative suddenness of the spore concentration in the air, and the rather high peak, are factors which in our experience with pollen have been found to render the antigen more harmful to patients.

3. The frequency of obtaining positive skin reactions in a routine series of patients with respiratory allergy is rather striking. Cases with symptoms of respiratory allergy during the rust and smut season showed the strongest positive reactions to rust and smut.

The marked antigenicity of the material is well demonstrated by the size of the wheals produced by the scratch and intradermal skin tests; by the occurrence of generalized reactions, and by the prompt reproduction of symptoms following inhalation of the spore powder.

In a recent communication Wittich [5] noted a marked prevalence of smut spores in Minneapolis in the latter part of the fall. He found that they originate in the vast grain storing centers of the Minneapolis district. In Detroit the exposed slides did not reveal smut spores at this late season.

Summary

1. A daily slide survey was made for spores of rust and smut. The curve exceeded in height the peak of the timothy curve and reached its maximum about July 23 and 30. The spore curve did not reach the height of the ragweed curve.

2. Among 106 consecutive cases of asthma and upper respiratory allergy, seven had symptoms exclusively at the rust and smut season, and 12 patients showed more or less severe exacerbations at that time.

3. The average intradermal skin reactions for rust and smut in these patients were compared graphically with reactions to other important antigens. Considerably stronger reactions to rust and smut occurred in the first two groups of patients, who exhibited symptoms at the time in question only.

4. In the two cases here reported an attempt was made to reproduce asthmatic attacks by inhalation of rust; this was accomplished without difficulties.

5. On the basis of the above findings, we consider sensitivity to rust and smut an important cause of seasonal allergy of the upper respiratory tract.

BIBLIOGRAPHY

1. FEINBERG, S. M.: Seasonal hayfever and asthma due to molds, Jr. Am. Med. Assoc., 1936 cvii, 1861.
2. WALDBOTT, G. L., ASCHER, M. S., and ACKLEY, A. B.: Relation of fungi to respiratory allergy. (To be published.)
3. CADHAM, F. T.: Asthma due to grain rusts, Jr. Am. Med. Assoc., 1924, lxxxiii, 27.
4. WITTICH, F. W., and STACKMAN, E. C.: Case of respiratory allergy due to inhalation of grain smuts, Jr. Allergy, 1936, viii, 189–193.
5. WITTICH, F. W.: Further observations on smut sensitivity. (To be published.)
6. DUKE, W. W., and DURHAM, O. C.: Pollen content of the air, Jr. Am. Med. Assoc., 1928, xc, 1529.
7. DURHAM, O. C.: Unusual shower of alternaria spores, Jr. Am. Med. Assoc., 1938, cxi, 24.
8. BROWN, G. T.: Hypersensitiveness to fungi, Jr. Allergy, 1936, vii, 455.
9. WALDBOTT, G. L., and ASCHER, M. S.: Optimal doses in pollen therapy, Jr. Allergy, 1937, viii, 457.

VON RECKLINGHAUSEN'S NEUROFIBROMATOSIS WITH BONE MANIFESTATIONS*

By Erich Uhlmann, M.D., and Abraham Grossman, M.D.,
Chicago, Illinois

There has been profound change in our conception of the disease originally described by von Recklinghausen in 1882 in his article on "Fibrome der Haut." For many years the disease was looked upon as a disorder of the peripheral nerves alone, especially of the cutaneous filaments. Multiple soft nodules of the skin (molluscum fibrosum) and the subcutaneous neurofibromata so frequently associated with them were considered the main attributes of the clinical condition. By 1901 Adrian had collected 407 cases, in many of which pigmentary changes had either anteceded or were coexistent with the formation of neurofibromata. The recognition of allied pigmentary disturbance raised some doubt as to the ectodermal nature of the disease. This was again questioned by Weiss, who in 1921 noted and commented on the scoliosis observed in 15 cases of von Recklinghausen's neurofibromatosis and suggested that bone changes would be found with increasing frequency in this disease. The classical paper of Brooks and Lehmann (1924) left no doubt as to the importance of bone changes in this condition and stamped it as a bizarre disease of protean manifestation rather than the simple cutaneous and subcutaneous neurofibromatosis described by von Recklinghausen.

The recent observation of two patients with von Recklinghausen's neurofibromatosis accompanied by unusual osseous changes prompts us to add these to the literature and to review the condition briefly with particular attention to its bony manifestations.

Case Reports

Case 1. M. H., a 16 year old school girl, first presented herself for examination at the Mandel Clinic of the Michael Reese Hospital on September 7, 1937. She complained of an enlargement of the right jaw of which she had first become aware at the age of six and which had continued to increase in size producing a marked facial asymmetry. There was no familial history of any similar condition nor was the patient aware of the existence of skin tumors, pigmentation or epilepsy in any of her relatives. The patient's intelligence was apparently somewhat less than the average for her age (at 16 she was still in the first grade of high school).

Upon examination her entire body was found to be covered with multiple flat café-au-lait spots of varying size (from 3 millimeters to 15 millimeters in diameter) and of varying intensity of pigmentation. These pigmented areas were particularly numerous over the face, neck, trunk and abdomen; the pigmentation of the extremities was less marked (figure 1). In the right axilla was an umbilicated, non-pigmented

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From the Tumor Clinic of the Michael Reese Hospital, Chicago, Illinois.

skin tumor of mushroom-like consistency measuring about 4 centimeters in diameter. Overlying the left elbow was a small subcutaneous nodule measuring one centimeter in diameter, freely movable and non-tender. The right mandible was considerably larger than the left; the soft tissues of the cheek and right submaxillary region, and the mucous membrane overlying the right lower alveolar process and the right side of the floor of the mouth were hypertrophied to a moderate degree (figure 2).

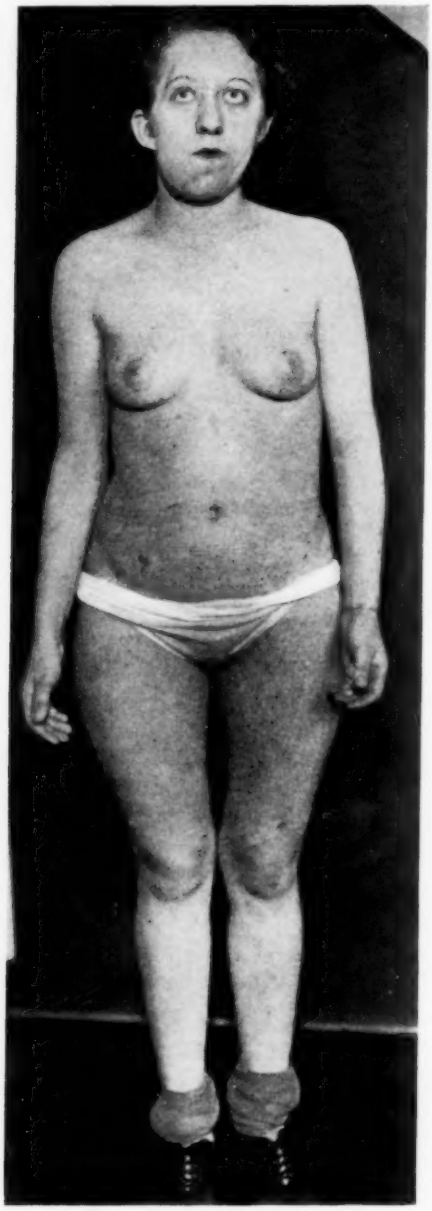

FIG. 1. Photograph of patient showing multiple café-au-lait spots, particularly over lower abdomen and upper thighs.

Roentgenogram of the right mandible taken on September 11, 1937 (figure 3) showed the molar teeth impacted into one another; the ramus was practically replaced by cystic loculi occupying the width of the bone from cortex to cortex leaving very little recognizable bony trabecular structure. Roentgenograms of the skull and of both hands showed no pathological findings.

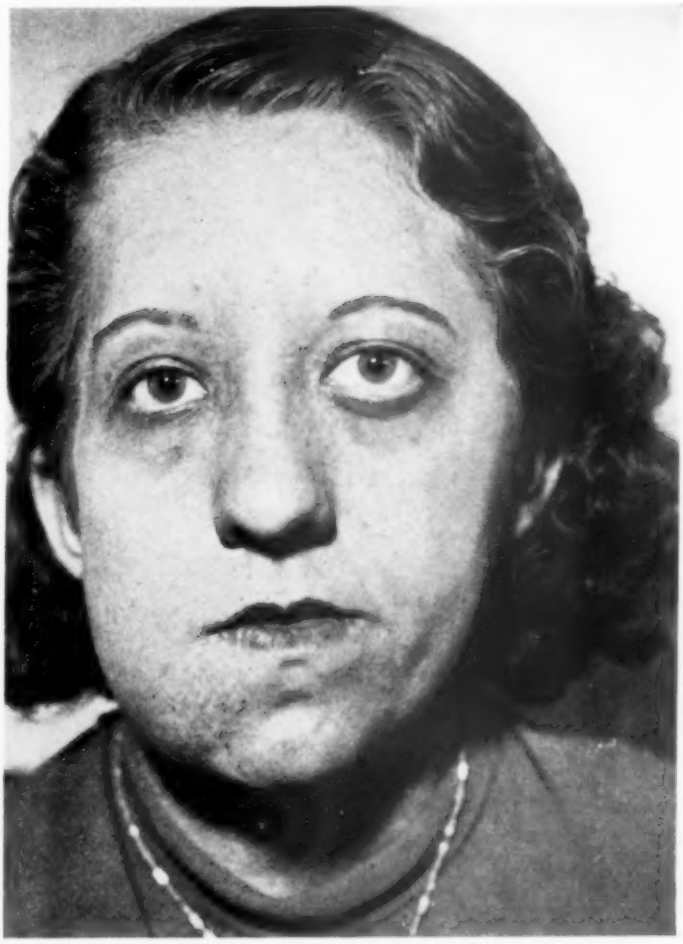

FIG. 2. Marked facial asymmetry due to enlargement of right mandible associated with von Recklinghausen's neurofibromatosis.

The blood Wassermann and Kahn tests were negative. The blood count was as follows: erythrocytes 4,660,000 with 80 per cent hemoglobin, leukocytes 10,200 with 74 per cent polymorphonuclear leukocytes and 26 per cent lymphocytes. The blood calcium was 11.8 mg. per 100 c.c., while the blood phosphorus was 4.5 mg. per 100 c.c. Urinalysis revealed no pathologic findings.

Histologic examination of the subcutaneous nodule overlying the left elbow revealed whorls of cells in parallel rows embedded in a moderately dense, fibrous connective tissue stroma. The individual cells were of spindle shape and of approximately the same size. The nuclei stained rather deeply and at times appeared vesicular.

The general structure was characteristic of neurofibroma. Biopsy of the jaw, performed through the oral surface on January 8, 1938, revealed similar histological characteristics (figure 4).

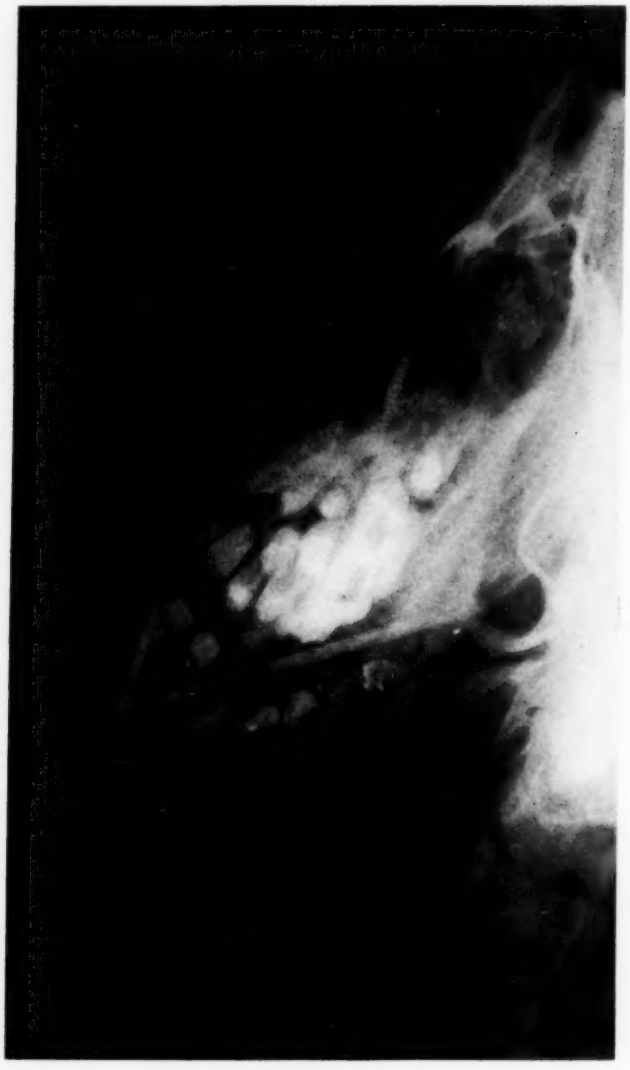

FIG. 3. Roentgenogram of right mandible showing cystic loculation and marked destruction of major part of ramus.

Extensive surgery for the jaw condition was thought to be contraindicated because of the benign nature of the lesion, the high incidence of local recurrence and the possibility of malignant metaplasia following surgery in these cases. Radiotherapy was not advised since these lesions are usually extremely radioresistant.

Case 2. R. G. was first brought to the Mandel Clinic of the Michael Reese Hospital on January 11, 1935, at the age of two, because of a progressive enlargement

of the left leg. When she was five months of age a few brown spots had appeared on the trunk and a more diffuse pale brown sheet-like pigmentation had been noted over the calf of her left leg. Shortly after this the left leg became heavier, fatter

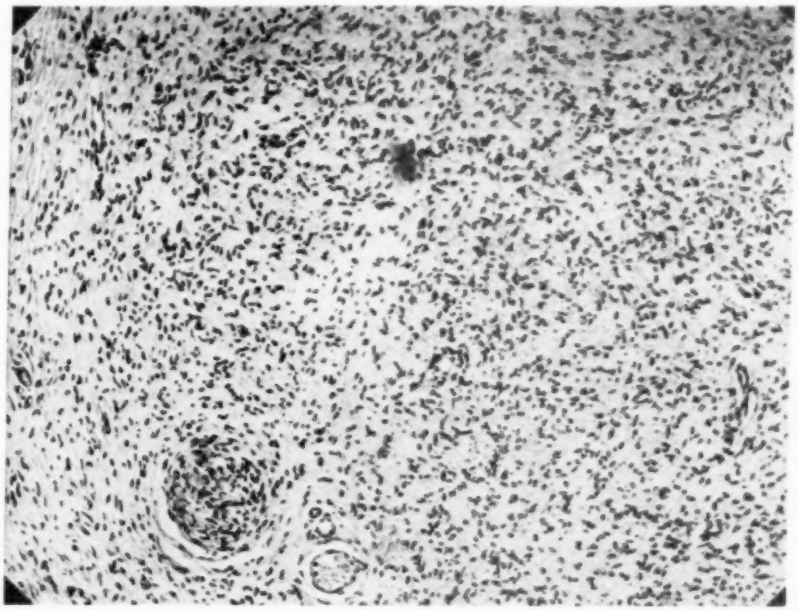

FIG. 4. Biopsy of right jaw. Magnification × 80. Whorls of cells are seen arranged for the most part in parallel rows embedded in a moderately dense fibrous connective tissue stroma. An occasional nerve ending is seen. The histological structure is typical of neurofibroma.

and slightly longer than the right. Both the mother and grandmother of the patient had diffuse patchy pigmentation of the skin and multiple pedunculated skin tumors characteristic of neurofibromatosis. In addition, the mother of the patient had a pachydermatocele of moderate size in the right supragluteal region (figure 5).

Examination of the patient revealed numerous circular and oval café-au-lait spots from 1 millimeter to 1 centimeter in diameter on the trunk and lower extremities. The left leg was considerably larger than the right and was covered on its antero-lateral and posterior aspects from knee to ankle by a confluent café-au-lait pigmentation (figure 6). The entire left leg from knee to ankle presented a diffuse subcutaneous nodularity of rope-like consistency. Measurements in vivo and by roentgenogram (figure 7) indicated that the left tibia was about 2 centimeters longer than the right. In addition, the roentgenogram showed an increased density with diffuse mottling and nodularity of the soft tissues of the leg.

The blood Wassermann and Kahn tests were negative. The blood cell count revealed 4,300,000 erythrocytes with 70 per cent hemoglobin, and 9,950 leukocytes with 68 per cent polymorphonuclear leukocytes, 30 per cent lymphocytes and 2 per cent eosinophiles. The urine test revealed no abnormal findings.

The condition was obviously that of von Recklinghausen's disease with gigantism of one leg associated with a marked neurofibromatosis of its soft tissues. Biopsy was thought to be contraindicated because of the risk of inducing malignant metaplasia thereby. Similarly, epiphyseal arrest by open operation, to check the accelerated disproportionate growth of the leg, was considered undesirable because of the danger

of cutting through neurofibromatous tissue. Consequently, radiotherapy was administered to the left upper and lower tibial epiphyses on the 4 gram radium pack in the attempt to delay the growth of the leg. The radiation was distributed over a period of two years, five cycles being given for a total of 60,000 milligram-hours to the lower

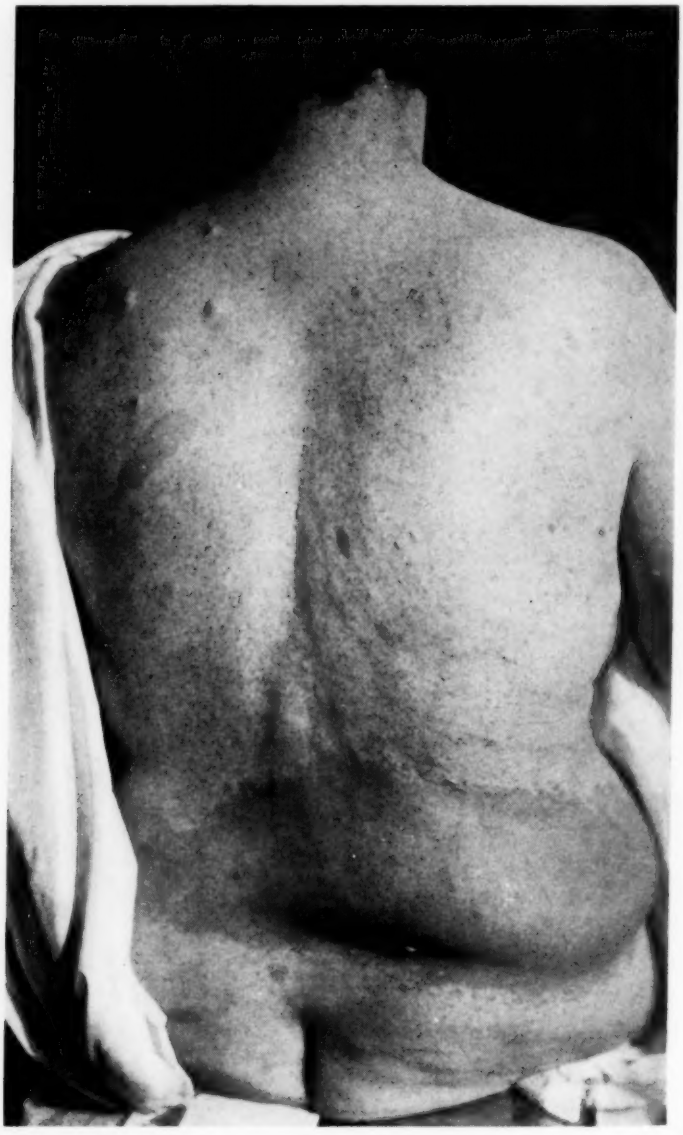

FIG. 5. Photograph of mother of our second patient showing generalized neurofibromatosis and pachydermatocele over right supragluteal region.

tibial epiphysis and 30,000 milligram-hours to the upper. Lateral and medial portals of entry, each measuring 6 by 8 centimeters, were employed at each epiphyseal zone. The skin-target distance was 10 centimeters; the filtration was 1 millimeter of platinum.

During each cycle the daily dosage varied from 500 milligram-hours to 1500 milligram-hours.

This quantity of radiation apparently had no effect on the subcutaneous neurofibromata nor did it retard the rate of growth of the leg. By November 20, 1937, the

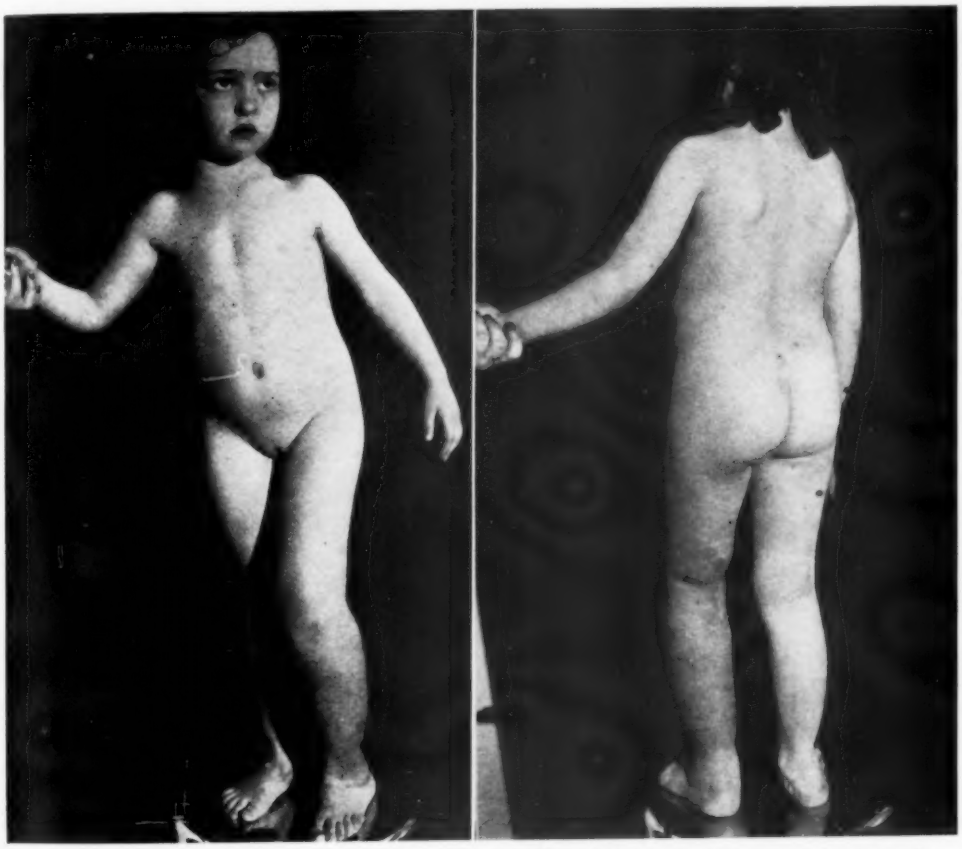

FIG. 6. Photograph of patient with diffuse café-au-lait pigmentation and hypertrophy of left leg associated with marked subcutaneous neurofibromatosis of this extremity. Note prominence in right supraclavicular fossa due to large cervicothoracic neurofibroma.

left tibia was 4 centimeters longer than the right as measured on the roentgenogram; the tibia had become bowed and the patient's limp was considerably more marked (figure 8).

In February 1938 the patient began to complain of pain and stiffness in the neck. A mass could be seen filling the right supraclavicular fossa and extending upwards to the level of the midportion of the sternocleidomastoid muscle (figure 6).

Roentgen-ray films of the cervicothoracic region (figure 9) at this time showed an egg-shaped soft tissue mass extending from the upper cervical region on the right to the level of the clavicle and across the midline, displacing the trachea markedly to the left. A smaller soft tissue mass could be seen at the base of the neck on the left. Lateral roentgenogram of the cervical spine (figure 10) showed a marked decalcification of the vertebral bodies in the region of the large cervical neurofibroma. These vertebral bodies showed a generally distorted contour and roughening of their

margins. The fifth cervical vertebra showed a particularly marked degree of roughening, with bony proliferation in the form of a spur-like projection from the anterior edge of this vertebral body. By July 1938 a moderate torticollis had developed.

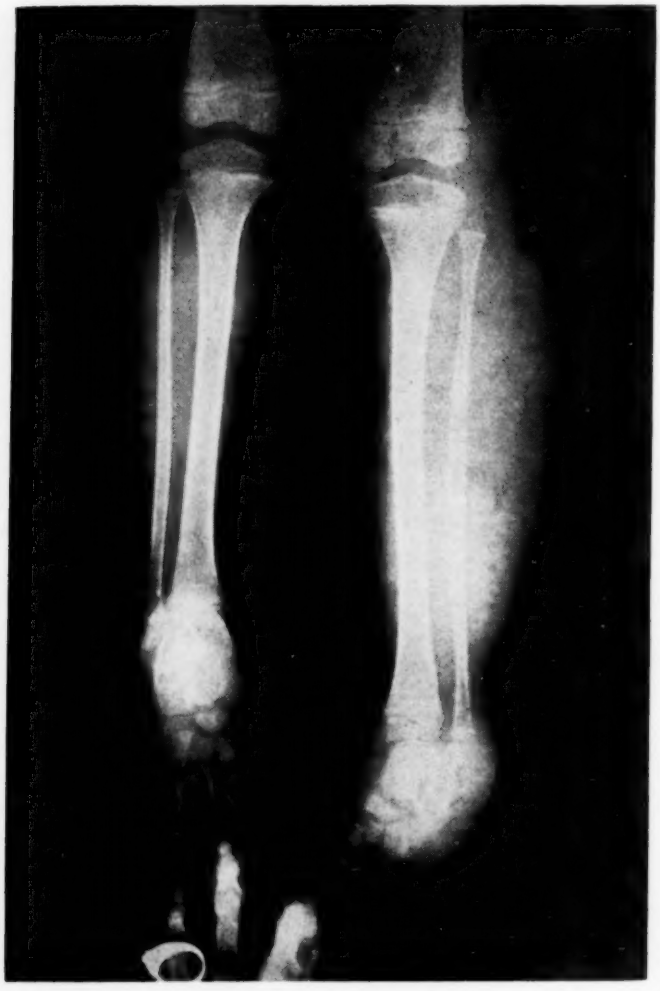

FIG. 7. Roentgenogram showing greater length of bones of left leg and diffuse neurofibromatosis of soft parts.

Radiation therapy was considered but thought inadvisable because of the radioresistant nature of neurofibromata and since the lesions of the left leg had not responded to previous radiotherapy. Surgery was likewise thought to be contraindicated at this time because of the rapid recurrence of cervicothoracic neurofibromata following operation (Epstein) and the reports in the literature of sarcomatous change following incomplete surgery for cervicomediastinal neurofibromata (Hosoi).

Review of the Literature

Fortunately, von Recklinghausen's neurofibromatosis is a rather rare condition. In 1901 Adrian was able to collect 407 cases from the literature.

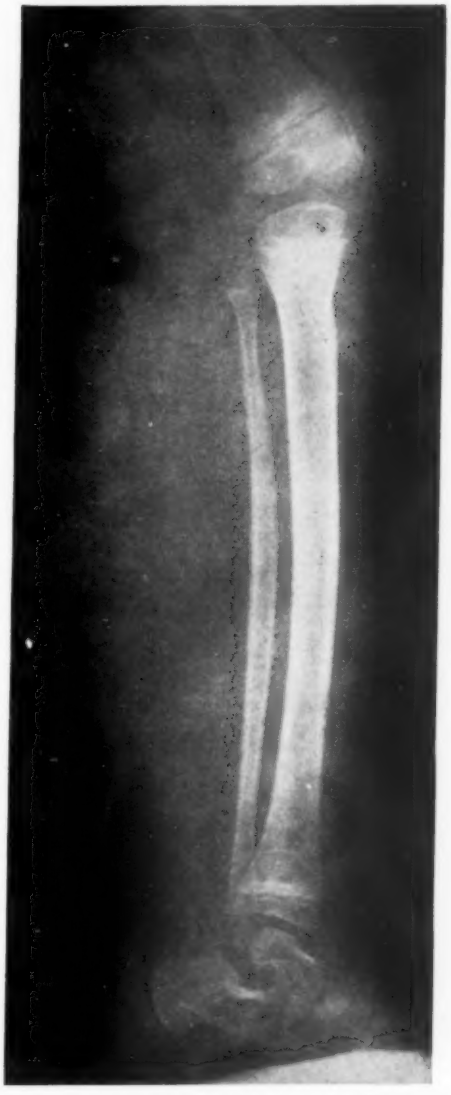

Fig. 8. Lateral roentgenogram shows anterior bowing of tibia hypertrophied in association with extensive neurofibromatosis of surrounding soft parts.

Smaller series have been reported by Stalmann and by Sharpe and Young (35 and 31 cases, respectively). Preiser and Davenport, in an exhaustive study of this condition, estimated its incidence in the general population as once in 2000. Among 4300 patients, with proved or suspected benign or

malignant neoplastic disease, referred to the Tumor Clinic of the Michael Reese Hospital in the past six years there have been seven with generalized neurofibromatosis. One must recall that many patients with this disease are never referred to general hospitals or clinics for neoplastic diseases since

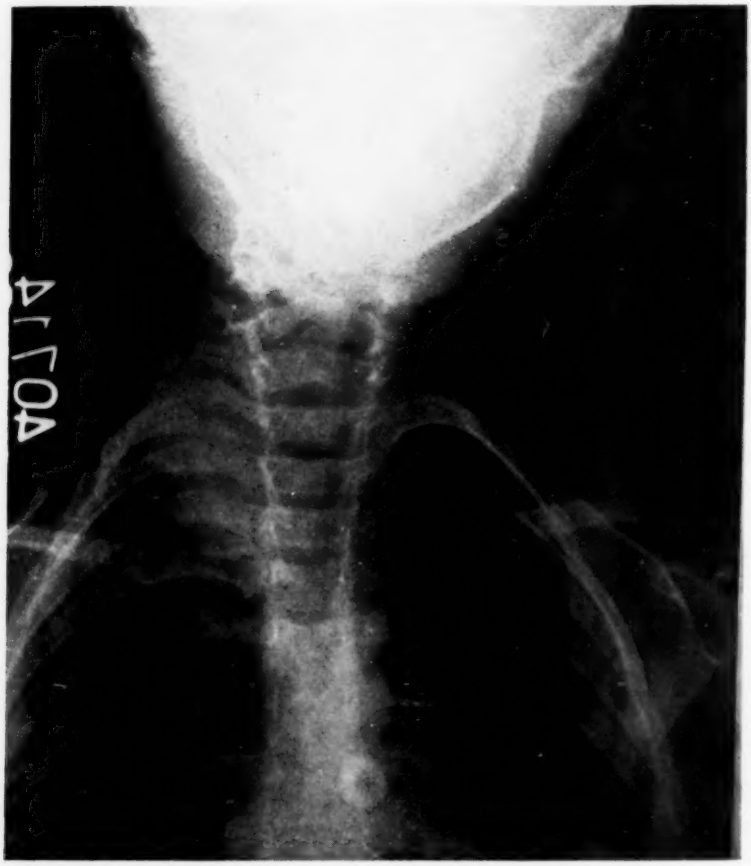

FIG. 9. Roentgenogram showing large cervical neurofibroma extending towards mediastinum and producing marked displacement of trachea.

there is so little to be offered therapeutically. The above figures, however, do suggest the relative infrequency of this condition.

According to Sharpe and Young there is no special geographic or racial distribution of the disease; it has been known to occur in the white, black, red and yellow races. Its incidence in the male is slightly higher than in the female. The condition has been observed in all age groups, the so-called formes frustes, characterized by pigmentation without tumor formation, being more common in infants and children.

There is undoubtedly a strong hereditary tendency associated with von Recklinghausen's neurofibromatosis. Preiser and Davenport, in a study of

115 offspring of 20 patients known to have generalized neurofibromatosis, found a like condition in 43.5 per cent. The development of the condition in the offspring bore no relation to the sex of the parent affected. These authors noted also a familial resemblance in the type and location of the pig-

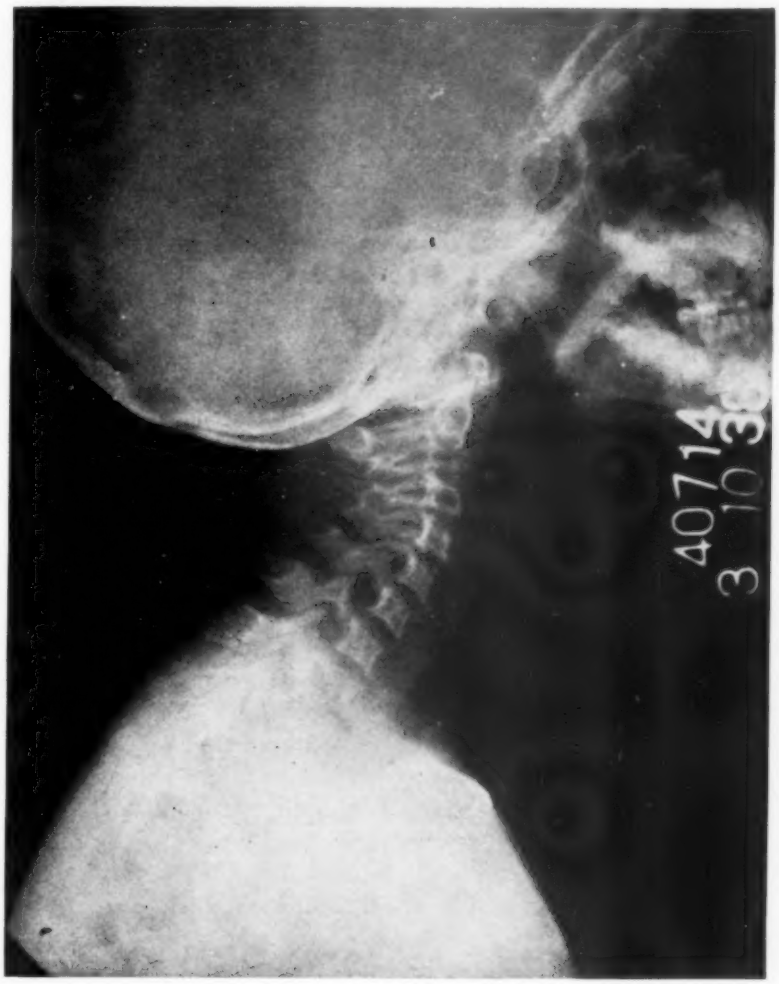

FIG. 10. Lateral roentgenogram of cervical spine showing decalcification, distortion and atrophy of cervical vertebral bodies adjoining a large cervical neurofibroma.

mentation and cutaneous tumors as well as in the tendency for sarcomatous metaplasia to occur.

One of us (Uhlmann) examined 60 members of three families in which cases of von Recklinghausen's neurofibromatosis had been diagnosed. Of these 60 individuals 13 were found to have the pigmentation and tumor formation characteristic of this disease. In one instance members of three

generations of one family, with a striking similarity of lesions, were observed. Five of the 13 patients exhibited osseous lesions which were mainly in the form of scoliosis and cystic changes of the skull.

A variety of congenital malformations have been reported in association with generalized neurofibromatosis. These include such conditions as cerebral meningocele, tuberous sclerosis, congenital glaucoma, spina bifida, defects and other anomalies of the fibula, ribs and other bones. In addition, imbecility and other mental defects, and psychogenic disturbances of many varieties have been observed in patients suffering from neurofibromatosis. Preiser and Davenport reported the existence of feeblemindedness in 7.8 per cent of 243 cases of von Recklinghausen's disease.

Considerable controversy exists as to the etiology of this condition. The consensus of opinion is that it is an embryological derangement, particularly of the ectoderm. The coincidence of allied bone changes suggests mesoblastic involvement as well. A number of endocrine disturbances associated with neurofibromatosis have been described, and such glands as the pituitary, thyroid and adrenals have been suspected of bearing some physiological relation to this disease. These associated endocrine disturbances include such conditions as acromegaly, Fröhlich's syndrome, Addison's disease, myxedema, cretinism, delayed and incomplete sexual development. Because of the frequency of pigmentation in this disease the adrenal gland particularly has been suspected of bearing some significance in the development of von Recklinghausen's disease. It is to be remembered that any of the endocrine glands may be displaced or compressed by neurofibromata resulting in corresponding endocrinological syndromes.

The clinical course of this disease is subject to a wide range of variation. In most instances there are pigmentary changes consisting of grayish-brown café-au-lait macular spots and patches of various patterns, sizes, shades and numbers. Such pigmentation usually appears at birth or in early infancy, often preceding the formation of skin tumors. The lesions are especially numerous over the trunk and occasionally appear to be distributed in rather symmetrical pattern bilaterally. The face and extremities are sometimes spared but usually exhibit a few lesions. At times the pigmentation assumes a broad confluent sheet-like expanse. The individual zones of pigmentation are not distinguishable grossly from the ordinary benign pigmented melanotic naevi occurring on many individuals. The significant histological finding in sections through such pigmented zones is the presence of multiple thickened nerve endings in parallel club-like strands in the upper layers of the derma. These strands are highly cellular, the nuclei being somewhat spindle-shaped.

Occasionally, pigmentation occurs alone without tumor formation; such cases are known as formes frustes. Generally, however, the pigmentary change is the precursor of tumor formation. Such tumors may be limited to the skin and subcutaneous tissues or may involve any of the other organs of the body.

The skin tumors are the most common and most striking attribute of von Recklinghausen's neurofibromatosis. The gross pattern of such lesions is extremely variable though the histological structure is the same. The most frequent variety is the so-called molluscum fibrosum or soft fibroma of the skin. These are found chiefly on the trunk and less often on the face and extremities. There is tremendous variation in the size and number of these tumors. There may be only a few or thousands; they may be as small as a millet-seed or as large as a man's head. These skin tumors may be sessile, slightly raised, or completely pedunculated. They are usually soft and at times somewhat compressible on palpation, often resting in cavities partly filled with fluid (this is usually associated with myxomatous degeneration of the neurofibroma). There is seldom any pain with such tumors. Rarely, severe pain does occur arising at the site of the skin tumor and radiating in the direction of the cutaneous nerves associated with the tumor in question. On section these neurofibromata are white or whitish-gray and rather translucent. According to Stalmann, who performed biopsies in 35 cases of von Recklinghausen's disease, there is no typical histological pattern. One often finds a palisade-like effect with the nuclei arranged in parallel longitudinal rows. The individual nuclei are elongated and irregular in outline, often containing chromatin resembling the nucleoli of nerve cells. There is considerable diversity of opinion as to the pathogenesis of these skin tumors. This has led to such terms as multiple neuroma, peripheral glioma, schwannoma, neurinoma and perineurial fibroblastoma for one and the same pathological entity. Most authors, however, believe that such tumors are fibromas arising from the connective tissue elements of nerves, particularly from the sheath of Schwann.

In addition to skin tumors, or not infrequently without visible skin tumors, neurofibromata may occur as bead-like subcutaneous nodules along the course of the peripheral nerve trunks. Such subcutaneous nodules are of varying size and distribution but occur most frequently in the neck or extremities. The peripheral nerves most often affected are the median and ulnar of the upper extremity and the sciatic in the lower extremity. These subcutaneous nodules have a rope-like or worm-like consistency and in the neck are often mistaken for cervical lymphadenitis. At times, the larger nerves, such as the spinal or even the cranial nerves, may be involved. The acoustic neuroma is of this type. The cauda equina is a not infrequent location for this variety of tumor. According to Camp, 23 per cent of all spinal cord tumors are neurofibromata. These tumors have also been known to involve the sympathetic and parasympathetic nerves. Histologically, the lesions are of the same structure as the pedunculated cutaneous neurofibromata.

At times the subcutaneous neurofibromatosis assumes an exaggerated contour producing a diffuse swelling of flounce-like nature. This variety of overgrowth is known as the plexiform neuroma, elephantiasis neuromatosa or pachydermatocele.

In addition, neurofibromatosis has been known to involve the visceral nerves, especially those of various parts of the gastrointestinal and genitourinary tracts.

Formerly considered a pathological process of rather stationary and quiescent character, this disease at times undergoes active and extensive metamorphosis. Usually the neurofibromata remain stationary in size or grow very slowly. Very rarely the lesions regress spontaneously. At times the pedunculated tumors undergo cystic or myxomatous change, and occasionally the blood supply of the pedicle is compromised and the tumor drops off. The disease may undergo particularly rapid alteration under such physiological stimuli as puberty and pregnancy. There may be slight regression in the size of the lesions at the menopause. Yakovlev and Guthrie particularly have pointed out the dynamic character of the disease with periods of exacerbation and remission in tumor growth. In addition, there is an acute fulminating form characterized by either extremely rapid proliferation and generalized dissemination of neurofibromata or sarcomatous degeneration with metastasis. LeBell maintains that benign neurofibromata undergo malignant transformation in from 12 to 20 per cent of cases following trauma or other irritation. This is in accord with the findings of Sharpe and Young to the effect that sarcomatous change occurs in 13 per cent of all cases. These authors further state that of the cases in which sarcoma develops, metastasis occurs in 22 per cent. Hosoi collected 65 instances of sarcomatous transformation in von Recklinghausen's neurofibromatosis and suggested the danger of inducing such metaplasia by biopsy or inadequate surgery for neurofibromata.

The osseous changes found associated with von Recklinghausen's neurofibromatosis are among the most interesting and often most serious manifestations of this condition. The recognition of such changes dates back to Gould who in 1918 had the opportunity of studying at autopsy the skeletal changes in a patient with generalized cutaneous and subcutaneous neurofibromatosis. A general osteoporosis and decalcification of the pelvis similar to that encountered in osteomalacic pelves was found. There was no replacement by fibrous tissue as is found in fibrocystic osteitis. The parathyroid glands and hypophysis were studied carefully but no histological changes were found.

In 1921, Weiss called attention to a second variety of bony pathology associated with this disease, namely scoliosis, which he observed in 15 patients with generalized neurofibromatosis. Brooks and Lehmann (1924) reported seven cases of von Recklinghausen's disease with bony changes which they considered characteristic of the disease. These changes were of three types: scoliosis, abnormalities of growth and so-called subperiosteal cysts. In two of their cases there was marked overgrowth of long bones (femur and tibia). When such overgrowth occurs it is usually in areas of elephantiasis. This may be due to periosteal hyperemia associated with the generally increased blood supply necessary to nourish such an elephantiasic

area. Such hypertrophy is circumferential as well as longitudinal and is analogous to the hypertrophy occurring in chronic osteomyelitis or congenital syphilitic periostitis described by Speed. In other cases, especially with pachydermatocele, there may be actual invasion of the bone by neurofibromata. Such involvement may vary from slight irregularity of periosteal or cortical structure to large tumors projecting from the surface of the bone or embedded within the substance of the bone as cyst-like cavities. Microscopic examination of these tumors in one of the cases reported by Brooks and Lehmann showed histologic structure similar to that of the skin tumors. When such neurofibromata actually invade the bone, the osteogenetic periosteum covering the tumor may produce a shell of bone around the tumor resulting in the so-called subperiosteal bone cyst. The radiological appearance of such pseudocysts resembles the findings in osteitis fibrosa cystica, giant cell tumor and xanthomatosis; at times it may be difficult or impossible to differentiate these lesions grossly even at open operation. The entire shaft of the bone may become soft, porous and plastic, with bowing or other deformities, as a result of diffuse neurofibromatous invasion. If the epiphyseal cartilage alone is invaded, shortening and atrophy will result. In isolated zones of periosteal neurofibromatosis, exostoses may develop. In cases with marked decalcification, pathological fractures may occur and heal with pseudoarthroses characteristic of osteopsathyrosis. Deformities such as coxa vara have been described frequently.

Lehmann has commented on the frequency of cystic changes in the skull. Palpable defects of the cranium beneath plexiform neuromas have been reported. Among other changes in the skull are thinning of the cranial vault, atrophy and aplasia of the mandible, maxilla and zygoma. The combination of atrophy and hypertrophy of the various facial bones may produce bizarre distortions, the appearance of leontiasis ossium being not infrequent.

According to Reuben, about 7 per cent of patients with neurofibromatosis show bony changes. Seven of the 31 patients observed by Sharpe and Young exhibited osseous involvement, this being in the nature of scoliosis in six of the seven cases. In six of the patients with bone changes reported by these authors the basal metabolic rate, dextrose tolerance, calcium and phosphorus content of the blood were determined and were found to be within normal limits.

The vertebral column is involved in about 43 per cent of the cases showing skeletal changes according to Miller. The most frequent vertebral change is scoliosis, kyphosis and kyphoscoliosis occurring somewhat less often. The most common site for such change is the lower thoracic spine. Vertebral involvement may be so extensive as to produce compression myelitis (Miller reported such a case with sarcomatous degeneration of the neurofibromata involving the vertebral column). The vertebral column is especially apt to be involved in the presence of neurofibromata of the spinal cord. Such tumors produce pressure on the underlying vertebral bodies with erosion, decalcification and changes in contour. In the thoracic region the ribs

are not infrequently affected similarly. The vertebral changes have been considered so characteristic by Camp as to enable him to localize the level of suspected cord tumors in 42 per cent of cases. According to him, the earliest change is erosion and flattening of the mesial border of the pedicle of the vertebra at the site of the tumor. Later one finds concave areas of erosion on the posterior or posterolateral aspect of the vertebral body itself as the neurofibroma enlarges.

It is to be pointed out that scoliosis may occur in those patients with inequality in length of the lower extremities even in the absence of neurofibromatous involvement of the vertebral column.

Summary

The authors have presented two cases of von Recklinghausen's neurofibromatosis with osseous changes. The one exhibited marked cystic changes in the mandible, the other gigantism and bowing of the tibia associated with elephantiasis of the lower extremity and osteoporosis, decalcification and atrophy and deformity of the cervical vertebrae in the region of a rapidly growing cervical neurofibroma.

The nature of the disease has been reviewed; it is to be considered of dynamic rather than stationary nature. At the present time no adequate treatment is available for this condition; surgery and radiation are both unsatisfactory. Diagnosis can generally be made without biopsy; in fact, biopsy may sometimes be a dangerous procedure in this condition because of the possibility of inducing sarcomatous metaplasia.

The frequency and seriousness of the bone changes encountered in association with von Recklinghausen's neurofibromatosis have been emphasized. In all cases of the disease, even in the formes frustes without clinical evidence of tumor formation, general roentgen-ray studies are recommended to detect latent osseous changes. Such radiological studies should include the skull, the entire vertebral column and all the bones of the upper and lower extremities.

BIBLIOGRAPHY

Adrian, C.: Über Neurofibromatose und ihre Komplikationen, Beitr. z. klin. Chir., 1901, xxxi, 1.

Brooks, B., and Lehmann, E. P.: The bone changes in von Recklinghausen's neurofibromatosis, Surg., Gynec. and Obst., 1924, xxxviii, 587.

Camp, J. D.: A roentgenologic study of the osseous changes with neurofibroma of the spinal cord and associated nerves, Proc. Staff Meet. Mayo Clin., 1933, viii, 239.

Epstein, N.: Neurofibromatosis with intrathoracic neurofibroma, New England Jr. Med., 1937, ccxvi, 551.

Gould, E. P.: The bone changes occurring in von Recklinghausen's disease, Quart. Jr. Med., 1918, xi, 221.

Hosoi, K.: Multiple neurofibromatosis with special reference to malignant transformation, Arch. Surg., 1931, xxii, 258.

LeBell, I. C.: Von Recklinghausen's neurofibromatosis in children, Arch. Pediat., 1937, liv, 454.

MILLER, A.: Neurofibromatosis with reference to skeletal changes, Arch. Surg., 1936, xxxii, 109.

PREISER, S. A., and DAVENPORT, C. B.: Multiple neurofibromatosis and its inheritance, Am. Jr. Med. Sci., 1918, clvi, 507.

REUBEN, M. S.: Von Recklinghausen's disease, Arch. Pediat., 1939, li, 522.

SHARPE, J. C., and YOUNG, R. H.: Recklinghausen's neurofibromatosis, Arch. Int. Med., 1937, lix, 299.

STALMANN, A.: Nerven-, Haut- und Knochenveränderungen bei der Neurofibromatosis Recklinghausen und ihre entstehungsgeschichtlichen Zusammenhänge, Virchow's Arch. f. path. Anat., 1933, cclxxxix, 96.

RECKLINGHAUSEN, F. VON: Über die multiplen Fibrome der Haut und ihre Beziehung zu den Neuromen, 1882, Berlin.

WEISS, R. S.: Curvature of the spine in von Recklinghausen's disease, Arch. Dermat. and Syph., 1921, iii, 150.

YAKOVLEV, P. I., and GUTHRIE, R. H.: Congenital ectodermoses in epileptic patients, Arch. Neur. and Psychiat., 1931, xxvi, 1145.

STUDIES IN PERNICIOUS ANEMIA: AN INQUIRY INTO THE RÔLE OF PEPSIN *

By Samuel Morrison, M.D., F.A.C.P., *Baltimore, Maryland*

In a paper on the mechanism of therapy in pernicious anemia, Greenspon [1] suggested that an "extrinsic factor" as conceived by Castle was unnecessary and that an antianemic principle protected from the inactivating effect of pepsin, such as beef (or other source of "extrinsic factor") was solely essential. This suggestion coincided with our belief that antipernicious anemia potency may be attributed to the fundus as well as to other portions of the stomach, and that this potency is ordinarily neutralized by the action of pepsin, a product primarily of the fundus. Greenspon's contention if confirmed will strongly support our belief.

It has been definitely established that a desiccated defatted hog stomach preparation (Ventriculin) has the distinctly antipernicious properties of Castle's "intrinsic factor." Meulengracht [2] has shown with defatted pulverized powders (dried at low temperature) prepared from cardiac, fundus, pyloric and duodenal glands, with muscularis, that the fundus gland preparation was inactive, the cardiac portion mildly active, and the pyloric and duodenal portions were strongly active in antianemic effect. Yet this pyloric gland powder (prepared commercially in Denmark as Pylorin) has about the same activity as Ventriculin, which is made from the entire stomach.

There are, therefore, two suggestive evidences to support the theory that fundus contains antianemic factor. First, whole stomach should be less potent than pyloric gland preparations if the fundus portion is inert, but this supposition has not been confirmed. Second, if Greenspon's concept of the action of pepsin be true, it may explain the apparent inactivity of the fundus portion. Both Ventriculin and Pylorin contain protein of the muscularis which acts as an adsorbent of pepsin according to Greenspon, or as a source of extrinsic factor according to Castle. These possibilities led us to repeat Greenspon's work using his depepsinized whole gastric mucosa and in addition, prepared in precisely the same manner, hog's stomach divided into cardiac, fundus and pyloric portions.

In the meantime several reports have appeared which do not substantiate Greenspon, but none definitely refuted the observation that pepsin could, at least partially, inactivate stomach preparations of established antianemic

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In pursuing these studies I have had the coöperation of Dr. Holmes of the University Hospital, Drs. Edwards and Myers of the Church Home and Infirmary, Drs. Rainy, Wyrens and DeSautelle of the City Hospitals, Dr. Freeman of the Mercy Hospital and Dr. Levi of St. Joseph's Hospital, Baltimore. Thanks are also due to Dr. Anderson, Director of the Squibb Laboratories, for his willingness to prepare and supply the depepsinized preparations used in these studies.

The expenses of this investigation were defrayed in part by a grant from the Julius Friedenwald Research Fund of the University of Maryland, School of Medicine.

potency. For example, Ungley and Moffett [3] found that peptically inactivated fundus mucosa of pig's stomach when administered with extrinsic factor gave negative results in two cases and a negative but inconclusive result in a third.

On the other hand, pylorus mucosa prepared similarly and administered with a source of extrinsic factor was effective in six cases. Furthermore, they found that orally administered depepsinized gastric juice and pepsin-free extracts of pylorus mucosa had little or no hematopoietic effect unless interaction with a source of extrinsic factor (e.g., autolysed yeast) was allowed. They accordingly concluded that adsorption of pepsin had no effect on extrinsic factor activity since no pepsin was present; also since autolysed yeast required interaction with normal gastric juice or pylorus extract which presumably contained pepsin, to render it effective for blood regeneration, that it probably acts as extrinsic factor and not because " it contains elements that are capable of stimulating the cells that elaborate the gastric anti-anemic agent or because these elements furnish material for the synthesis of the latter " as Greenspon had suggested.

In short, these authors (1) reaffirmed the necessity for both intrinsic and extrinsic factors in hematopoiesis, (2) demonstrated that depepsinized fundus even with extrinsic factor was probably hematopoietically inactive, and (3) that pylorus, under the same conditions, was potent. Conclusive as these experiments appear to be, however, there are two differences between them and the work of Greenspon: the method of preparation of the depepsinized products, and the failure of Ungley and Moffett to use whole stomach mucosa for control as Greenspon had done.

Hanes, Hansen-Prüss and Edwards [4] suggested that the gastric juice feeding experiments could be vitiated by the presence of extrinsic factor in the stomach of the patient or in the gastric juice of the donor. They fed neutralized and chilled gastric juice to five untreated patients with pernicious anemia and observed no hematopoietic potency, but these observations alone would not disprove Greenspon's entire thesis.

A corollary investigation was Fitz-Hugh and Creskoff's [5] study of the effects of depepsinized human gastric juice administered orally and intramuscularly. They point out that Greenspon's patients were not submitted to a (12 hour) fast, that gastric lavage did not immediately precede the gastric juice collections, that the recipients did not receive gastric lavage prior to the administration of gastric juice, and that they were fed too soon (four hours) after gastric juice feedings. Observing these precautions, Fitz-Hugh and Creskoff substantiated neither Morris and co-workers nor Greenspon, as regards the sole importance of " intrinsic factor." They believe, however, that Greenspon is possibly correct in his conclusion that peptic digestion destroys " Ventriculin."

Castle and Ham [6] in their recent " recheck " studies, followed Greenspon's technic except that no ice was put into the gastric juice. They believe that the diet in the patient of Greenspon who responded to neutralized gastric

juice probably contained extrinsic factor which would interact in the period of four hours with the intrinsic factor. They concluded that "normal human gastric juice does not contain an 'anti-pernicious anemia principle' effective on oral administration without contact with food (extrinsic) factor." In another experiment they sustained Greenspon's belief in the destructive action of peptic hydrolysis on an "anti-pernicious anemia principle" because a two hour period of incubation with pepsin was detrimental to intrinsic factor. However, they believe that since removal of pepsin without change in other properties of the gastric juice was not undertaken, their observations do not permit definition of the nature of the destructive process as necessarily peptic hydrolysis. Moreover, they showed that beef muscle and gastric juice administered without opportunity for contact (12 hours) were wholly ineffective.

The Method of Inquiry

The present investigation was so planned that the above criticisms of Greenspon's work could be avoided. Furthermore, it was hoped that the validity of Greenspon's hypothesis could be tested with less error and fewer variables if we used depepsinized gastric mucosa, instead of concentrating on gastric juice. Especially so, since the major part of Greenspon's claim was based on results obtained with it. Our plan was to give depepsinized gastric mucosa orally to a patient whose diet excluded extrinsic factor and then to repeat the experiment with a diet containing adequate extrinsic factor. In so doing, evidence regarding the relative importance of the anti-pernicious anemia principle, intrinsic and extrinsic factors, would be observed, and the importance of pepsin might be surmised. Such an approach we hoped would establish or refute Greenspon's hypothesis. We then planned to carry our observations a step further by attempting to determine the hematopoietic potency of various portions (fundus and pylorus) of the stomach, alone and with the addition of extrinsic factor.

The four patients available for study were typical cases of Addisonian pernicious anemia. All of them were women (ages 64, 53, 50 and 48), all gave evidence of cord changes, and none had been treated. In one (age 48) the cord changes seemed so progressive that liver extract was given before any oral therapy was tried. Her reaction (chart 2) to liver intramuscularly was considered a control with which comparison of the others could be made, inasmuch as the patients were alike even to the degree of anemia. The integrity of intestinal permeability had to be proved, as well as the adequacy of intrinsic and extrinsic factors, before results could be considered of value and we therefore estimated any response to depepsinized oral therapy by comparison with the response to an oral preparation of known potency. This was not always possible but the experiments were so arranged that all observations were cross-checked and in practically every instance the three factors (intrinsic factor, extrinsic factor and intestinal absorption) could be carefully evaluated.

TABLE I

Comparison of the Effect of Mucex * with and without Extrinsic Factor

Days of Treatment	(Patient—I. W.) Without Extrinsic Factor in Diet				(Patient—E. W.) With Extrinsic Factor in Diet			
	Red Blood Cells Millions	Hemoglobin Per Cent	Reticulocytes Per Cent	Treatment	Red Blood Cells Millions	Hemoglobin Per Cent	Reticulocytes Per Cent	Treatment
1			1.1	Basal Diet	2.49	70	0.5	Basal Diet
2			1.8	Basal Diet			0.8	Basal Diet
3	2.61	68	0.5	Basal Diet			1.4	Basal Diet
4			1.3	Basal Diet			1.0	Basal Diet
5			0.5	Basal Diet				Basal Diet
6			1.1	Basal Diet + 20 gm. Mucex q.d.			0.9	Amplified Diet
7			2.0	Basal Diet + 20 gm. Mucex q.d.	2.0			Includes Ext. Factor
8			2.1	Basal Diet + 20 gm. Mucex q.d.		65	1.4	Includes Ext. Factor
9			3.8	Basal Diet + 20 gm. Mucex q.d.			1.8	Includes Ext. Factor + 20 gm. Mucex q.d.
10			2.5	Basal Diet + 20 gm. Mucex q.d.			1.4	Includes Ext. Factor + 20 gm. Mucex q.d.
11		67	3.2	Basal Diet + 20 gm. Mucex q.d.	2.0		1.8	Includes Ext. Factor + 20 gm. Mucex q.d.
12			1.0	Basal Diet + 20 gm. Mucex q.d.		74	1.5	Includes Ext. Factor + 20 gm. Mucex q.d.
13			0.9	Basal Diet + 20 gm. Mucex q.d.				Includes Ext. Factor + 20 gm. Mucex q.d.
14			1.8	Basal Diet + 20 gm. Mucex q.d.			1.3	Includes Ext. Factor + 20 gm. Mucex q.d.
15			2.0	Basal Diet + 20 gm. Mucex q.d.			1.6	Includes Ext. Factor + 20 gm. Mucex q.d.
16				Basal Diet + 20 gm. Mucex q.d.	2.58		1.5	Includes Ext. Factor + 20 gm. Mucex q.d.
17			1.4	Basal Diet + 20 gm. Mucex q.d.		70	1.1	Includes Ext. Factor + 20 gm. Mucex q.d.
18	2.63	68	0.8	Amplified Diet Extrinsic Factor Added			0.8	Includes Ext. Factor + 20 gm. Mucex q.d.
19			1.0	Amplified Diet Extrinsic Factor Added	2.01	62		Includes Ext. Factor
20			0.9	Amplified Diet Extrinsic Factor Added				Includes Ext. Factor
21	2.65	69	2.0	Amplified Diet Extrinsic Factor Added	2.2	66	0.7	Includes Ext. Factor

* Mucex is the name given Greenspon's depepsinized whole stomach mucosa.

The administration of mucex over a period of 10 days—20 grams each day, does not produce a reticulocyte response in patient E. W. whose diet contained sources of extrinsic factor (adequate beef and other foods with the exception of those containing intrinsic factor). The reticulocyte response in patient I. W., whose diet was lacking in sources of extrinsic factor, is neither marked, orderly nor maintained and is not followed by a rise in hemoglobin or red blood cells during a period of observation considerably longer than is shown.

Experiment 1. Depepsinized gastric mucosa "Mucex," was secured from the Squibb Laboratories with the consent of Dr. Greenspon and the coöperation of its Director, Dr. Anderson. The dosage advised was 20 gm. a day. In table 1 are recorded the results of such therapy in a patient on a basal diet (as advised by Castle)

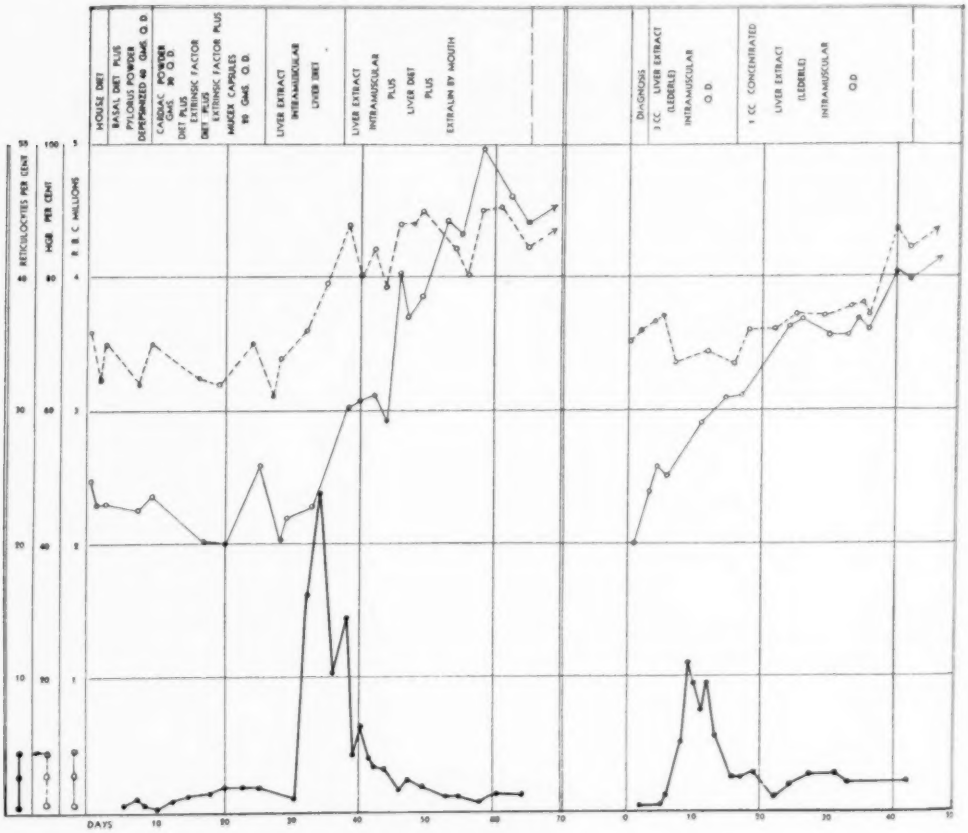

CHART 1. (*Left*). Patient—E. W.—Age 64.
CHART 2. (*Right*). Patient—N. S.—Age 48.

excluding every possible source of extrinsic factor. In this instance it was found unnecessary to adhere to the 12 hour interval between feedings although we began by taking that precaution. Compared to these values are those obtained in the second case in which exactly the same procedure was followed except that in the second case the diet contained extrinsic factor, beef, twice daily. No significant reticulocyte response followed in either case nor was there any elevation in hemoglobin or the red blood cell count. The unsustained response in patient I. W. was probably without significance. Assuming dosage was adequate it seems safe to deduce from these observations that depepsinized gastric mucosa prepared from the whole stomach does not contain any antipernicious anemia potency either with or without the addition of extrinsic factor. However, before such a conclusion could be reached the factor of intestinal absorption must be established. As seen in chart 1 this was not possible in patient E. W., in whom postponement of intramuscular liver extract was not justified in view of the cord changes. Her response to liver was characteristic and she has been able to maintain her count by oral "Extralin." This patient may be con-

sidered a test case. It is interesting to note that her response (*23.7* per cent reticulocytes) to intramuscular liver exceeds the expected maximum suggesting that perhaps preceding therapy may possibly have been partly responsible by either conditioning the blood-forming tissues, or by its own delayed reaction.

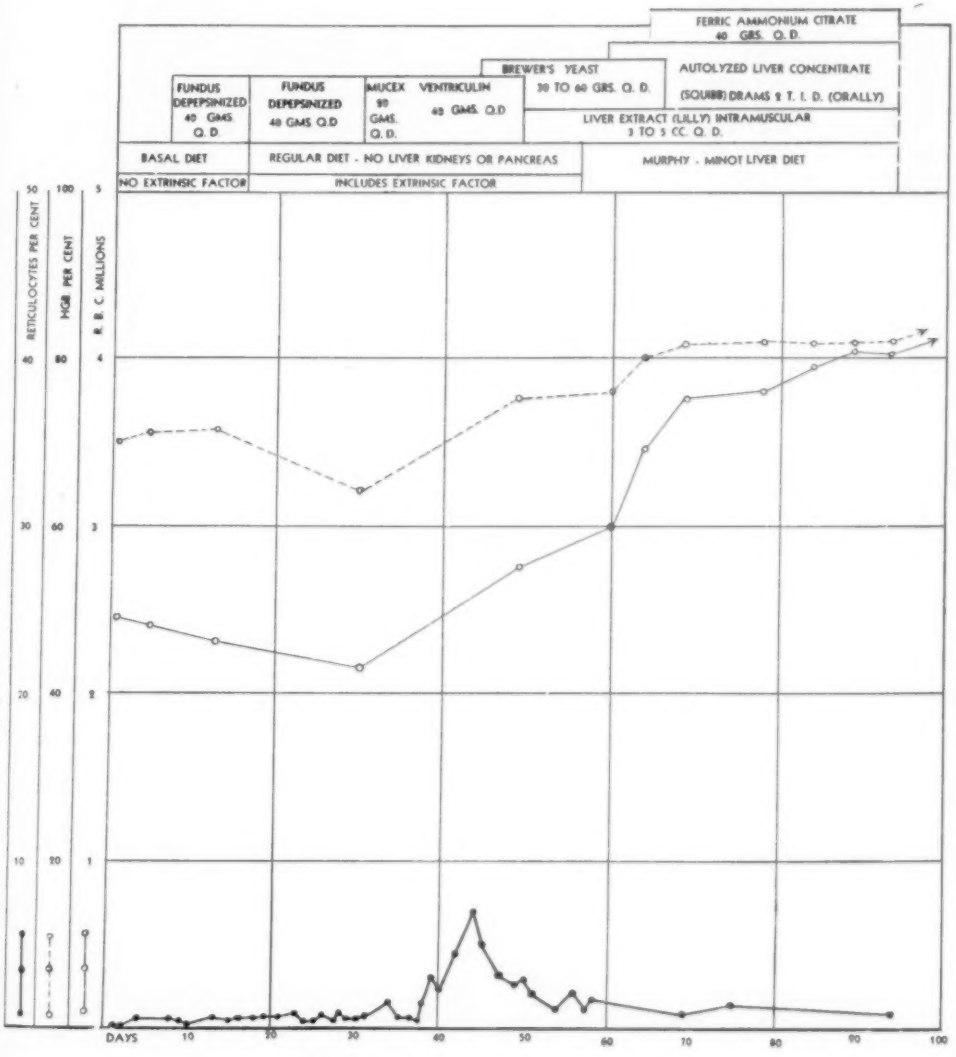

CHART 3. Patient—A. T.—Age 53.

In patient I. W., an interesting observation was recorded (chart 4). Her reticulocyte response to submaximal doses of Ventriculin and oral powdered liver extract were submaximal and these responses were not followed by subsequent characteristic rises in hemoglobin and red blood cell count although the latter may have been prevented by discontinuing therapy for a short period so that the reticulocyte gauge of therapeutic activity might be retained. Moreover, the response to liver extract intramuscularly was delayed and submaximal. All of these submaximal responses may be

significant when interpreted in terms of the comparative antipernicious anemia activity of the various preparations used. Nevertheless, the absence of a response to "Mucex" in the presence of extrinsic factor is presumptive evidence that there would hardly be a response when extrinsic factor was absent.

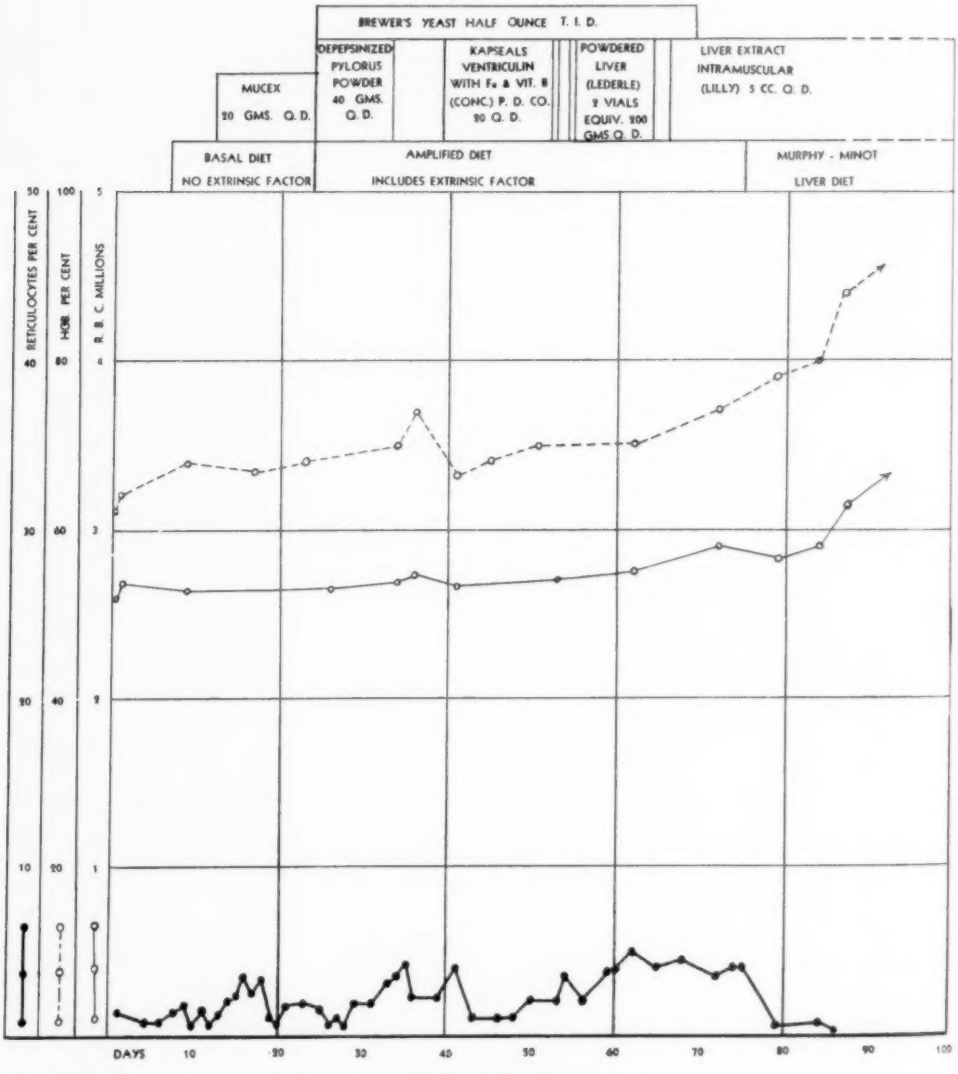

CHART 4. Patient—I. W.—Age 50.

Experiment 2. Mucosa stripped from the pylorus of the hog's stomach, observing all precautions for preserving the antianemic factor, was depepsinized according to Greenspon's method. Adequate amounts were fed to two patients; in the diet of one there was a source of extrinsic factor whereas in the other there was none. The data are recorded in table 2. In the latter, patient E. W., there was no reticulocyte response. However, she regurgitated a portion of the first dose (40 gm.) of pylorus

TABLE 1
Comparison of the Effect of Depepsinized Pyloric Mucosa with and without Extrinsic F

TABLE II

Comparison of the Effect of Depepsinized Pyloric Mucosa with and without Extrinsic Factor

Days of Treatment	Patient—E. W. Without Extrinsic Factor				Patient—I. W. With Extrinsic Factor			
	Red Blood Cells Millions	Hemoglobin Per Cent	Reticulocytes Per Cent	Treatment	Red Blood Cells Millions	Hemoglobin Per Cent	Reticulocytes Per Cent	Treatment
1	2.48	72		House Diet	2.62			
2	2.30	68		House Diet		68	2.0	Basal Diet
3	2.29	70		House Diet				Basal Diet
4				Basal Diet + Depep. Pylorus 40 gm. q.d.	2.63		1.4	Basal Diet
5			0.5	Basal Diet + Depep. Pylorus 40 gm. q.d.		68	0.8	Amplified Diet (Includes Ext. Factor) + Depep. Pylorus 40 gm. q.d.
6			0.7	Basal Diet + Depep. Pylorus 40 gm. q.d.			1.0	Amplified Diet (Includes Ext. Factor) + Depep. Pylorus 40 gm. q.d.
7				Basal Diet + Depep. Pylorus 40 gm. q.d.			0.9	Amplified Diet (Includes Ext. Factor) + Depep. Pylorus 40 gm. q.d.
8	2.2	63	0.3	Basal Diet + Depep. Pylorus 40 gm. q.d.			2.0	Amplified Diet (Includes Ext. Factor) + Depep. Pylorus 40 gm. q.d.
9			0.5	Basal Diet + Depep. Pylorus 40 gm. q.d.			2.0	Amplified Diet (Includes Ext. Factor) + Depep. Pylorus 40 gm. q.d.
10	2.49	70	0.5	Basal Diet + Depep. Pylorus 40 gm. q.d.				Amplified Diet (Includes Ext. Factor) + Depep. Pylorus 40 gm. q.d.
11			0.8	Basal Diet + Depep. Pylorus 40 gm. q.d.	2.67		3.3	Amplified Diet (Includes Ext. Factor) + Depep. Pylorus 40 gm. q.d.
12			1.4	Basal Diet + Depep. Cardia* 40 gm. q.d.		70	3.5	Amplified Diet (Includes Ext. Factor)
13			1.0	Basal Diet + Depep. Cardia* 40 gm. q.d.	2.71		4.3	Amplified Diet (Includes Ext. Factor)
14				Basal Diet + Depep. Cardia* 40 gm. q.d.		74	2.0	Amplified Diet (Includes Ext. Factor)
15			0.9	Amplified Diet (Includes Ext. Factor)				Amplified Diet (Includes Ext. Factor)
16	2.0	65	1.4	Amplified Diet (Includes Ext. Factor)				Amplified Diet (Includes Ext. Factor)
17			1.8	Amplified Diet (Includes Ext. Factor)			2.0	Amplified Diet (Includes Ext. Factor)
18			1.4	Amplified Diet (Includes Ext. Factor)				Amplified Diet (Includes Ext. Factor)
19			1.8	Amplified Diet (Includes Ext. Factor)	2.65	66	4.0	Amplified Diet (Includes Ext. Factor)
20	2.0	74	1.5	Amplified Diet (Includes Ext. Factor)				Amplified Diet (Includes Ext. Factor)
21							1.0	Amplified Diet (Includes Ext. Factor)
22			1.3	Amplified Diet (Includes Ext. Factor)				Amplified Diet (Includes Ext. Factor)
23			1.6	Amplified Diet (Includes Ext. Factor)				Amplified Diet (Includes Ext. Factor)
24			1.5	Amplified Diet (Includes Ext. Factor)			1.0	Amplified Diet (Includes Ext. Factor)
25	2.58	70	1.1	Amplified Diet (Includes Ext. Factor)				Amplified Diet (Includes Ext. Factor)
26			0.8	Amplified Diet (Includes Ext. Factor)		68	1.0	Amplified Diet (Includes Ext. Factor)
27				Amplified Diet (Includes Ext. Factor)				Amplified Diet (Includes Ext. Factor)
28	2.01	62		Amplified Diet (Includes Ext. Factor)			2.0	Amplified Diet (Includes Ext. Factor)
29				Amplified Diet (Includes Ext. Factor)				Amplified Diet (Includes Ext. Factor)
30	2.2	66	0.7	Amplified Diet (Includes Ext. Factor)	2.67	69	2.0	Amplified Diet (Includes Ext. Factor)

* Cardia depepsinized mucosa was used because supply of pyloric material could not be replenished in time.

The administration of depepsinized pylorus mucosa to patient E. W. whose diet did not include extrinsic factor, did not produce a reticulocyte response. On one occasion this patient regurgitated a portion of the material. This fact added to the substitution of cardia for pylorus material makes it desirable to repeat these observations. In the case of I. W., a small reticulocyte response is noted. This, together with the slight elevation in red blood cells and hemoglobin values must be interpreted as indicative of a minimal antipernicious anemia potency.

TABLE III

Comparison of the Effect of Depepsinized Fundus Mucosa with and without Extrinsic Factor

Patient—A. T.

Days of Treatment	Red Blood Cells Millions	Hemoglobin Per Cent	Reticulocytes Per Cent	Treatment
1	2.45	70	0	Basal Diet
2			0.1	Basal Diet
3			0.2	Basal Diet
4				Basal Diet
5	2.4	71		Basal Diet
6			0.3	Basal Diet + Depep. Fundus 40 gm. q.d.
7			0.2	Basal Diet + Depep. Fundus 40 gm. q.d.
8			0.15	Basal Diet + Depep. Fundus 40 gm. q.d.
9			0.1	Basal Diet + Depep. Fundus 40 gm. q.d.
10			0.2	Basal Diet + Depep. Fundus 40 gm. q.d.
11				Basal Diet + Depep. Fundus 40 gm. q.d.
12	2.3	71	0.4	Basal Diet + Depep. Fundus 40 gm. q.d.
13				Basal Diet + Depep. Fundus 40 gm. q.d.
14			0.2	Basal Diet + Depep. Fundus 40 gm. q.d.
15			0.3	Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
16				Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
17			0.2	Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
18			0.4	Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
19				Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
20			0.3	Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
21				Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
22			0.9	Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
23			0.3	Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
24			0.2	Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
25			0.5	Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
26			0.3	Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
27			0.7	Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
28			0.4	Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
29	2.18	64	0.3	Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
30			0.4	Amplified Diet Includes Ext. Factor + Depep. Fundus 40 gm. q.d.
31				Amplified Diet
32				Amplified Diet
33			1.5	Amplified Diet
34			0.4	Amplified Diet
35			0.8	Amplified Diet
36			0.5	Amplified Diet

The administration of depepsinized fundus mucosa, prepared by Greenspon's process, in large dosage over a sufficiently long trial period produces no rise in reticulocytes regardless of the presence or absence of extrinsic factor from the diet. In this patient the numerical value of hemoglobin and red blood cells decreased slightly, and the subjective symptoms became more disturbed.

powder administered and only received it for seven days (sufficient according to Greenspon) when, due to an inability to replenish our supply, we were forced to substitute cardia powder for the remaining trial period. This patient responded to liver extract intramuscularly and was maintained on Extralin (chart 1).

In the case of patient I. W., whose diet contained at least two sources of extrinsic factor (beef and brewer's yeast) pyloric powder was fed as seen in table 2 over a period of seven days. On the ninth day before any other therapy had been begun, the reticulocytes had risen in an orderly manner to a peak of 4.3 per cent. This is dis-

tinctly a submaximal response and was followed by a minor increase in red cell count and hemoglobin which can be interpreted as manifesting the presence of some antipernicious anemia potency. This patient also responded submaximally to both Ventriculin and oral powdered liver of known potency (chart 4). The experiment suggests that pylorus powder is not potent in the absence of extrinsic factor, and is potent with it.

Experiment 3. Depepsinized fundus mucosa was administered to patient A. T., without extrinsic factor. The results are recorded in table 3. There was no reticulocyte response and no change in either hemoglobin or red cell count. After this negative response an amplified diet including extrinsic factor was given and the depepsinized fundus substance was continued, without effect. There was, however, a satisfactory reticulocyte response (7 per cent) to Ventriculin (chart 3), and intestinal absorption was apparently satisfactory.

Discussion

Intestinal permeability is an extremely important, and perhaps uncertain, factor in determining the potency of oral preparations. The amount of material administered cannot by any means be considered the amount absorbed, for not only may there be a defect in intestinal absorption but diarrhea or vomiting may impair its effectiveness. Depepsinized preparations were extremely unpleasant in taste and smell. Perhaps the intestine may have reacted to them as foreign bodies in the unrefined form in which they were administered and have rejected them. Only " Mucex " was administered in capsules, the others in " revolting " powders.

The failure to disclose significant antipernicious anemia potencies in any of these depepsinized preparations should be considered not only in terms of insufficient intrinsic factor and extrinsic factor, but also in terms of intestinal impermeability. Any deficiency in the latter interferes with the absorption of both factors and also of antipernicious anemia principle, if such it be. Moreover the method of preparation of those materials, though yielding the potent products described in Greenspon's original report, may conceivably be responsible for the total or partial inactivity of these later preparations. This was suggested by Lim [7] whose work on gastrin seems applicable here and worthy of recalling. Lim found that the activity of the extracts in producing gastric secretion depended in a measure on their mode of preparation and he concluded that the potency of extracts of the mucous membrane of the stomach and small intestine is of the following decending potency: pyloric, cardiac, duodenal, fundic, jejunal and ileal. Pyloric extracts almost invariably produced the standard effect, cardiac and duodenal extracts sometimes, and the other extracts never. This is an important observation in the light of Meulengracht's recent work. The observations of Edkins and Maydell are mainly confirmed by Lim, while those of Popielski and others are not refuted. Indeed, it seems probable that, by adopting different methods of extraction, the order of potency could be so altered as to obtain results similar to those of Popielski, who found fundus extracts to be as active as those of the pylorus.

Although Meulengracht reported antipernicious anemia potency in the entire pyloric-gland region (including cardia and duodenum), Henning and Brugsch,[8] using only mucosa (Meulengracht's preparations contained mucosa plus muscularis) conclude from their investigations that powder prepared from the mucous membrane of the antrum was far superior to those from the cardia, fundus and duodenum and in fact the latter group did not produce any reticulocytosis. Gutzeit and Herrmann[9] found that powder from the fundus mucosa of hog's stomach caused a reticulocyte rise in pernicious anemia more regularly than powder prepared from pyloric mucosa. Moreover, Henning and Stieger[10] reported that by trying the mucous membrane of the body of the stomach and that of the pylorus separately they found both possessed the same blood regenerating power, and by proving that neither the one nor the other possessed a peptic ferment of any account in vitro, they believed they had confirmed the assumption that the effect of the powder was independent of peptic digestion or protein and was a primary and direct one on blood regeneration. It was as late as 1934 that Henning[11] definitely concluded that the pyloric antrum produced a substance which, in normal individuals, prevented the development of pernicious anemia.

Of further interest is Lim's consideration of whether or not the pyloric principle which he investigated is identical with histamine. It seemed likely to him, as it did to Keeton, Koch and Luckhardt, that the pyloric principle, or gastrin, is closely allied to histamine; at least the effect on the gastric secretion and motility is remarkably similar. Furthermore, Lim believes that "the localization of the excitant mainly in the pylorus and to some extent in the cardia and duodenum suggests a correlation between the distribution of the excitant and the histological structure. The cardiac and pyloric glands are, according to Bensley and others, identical in structure, while Brunner's glands in the duodenum are considered vagrant pyloric elements. These are composed entirely of 'mucoid cells' and it seems not unlikely that the gastric excitant has been extracted from these elements. Mucoid cells also occur in the walls of the fundus glands, but here they are fewer in number as they are mingled with peptic and oxyntic cells. This admixture may be the reason why fundus extracts, made by the simple procedures described here, were comparatively inert, while the more complex extractions employed by Popielski, Keeton and Koch may account for the success which they obtained, with their fundus preparations." Although Lim was not even remotely concerned with the subject of pernicious anemia his description of the pyloric principle and the anatomical relationships of the various portions of the gastro-duodenal region is so strikingly similar to that of Meulengracht that one is led to conclude that fundamentally the problem is basically the same in each instance.

Summary

According to Greenspon, pepsin is antagonistic to the antipernicious anemia factor in stomach (Castle's "intrinsic factor"). Pepsin is pre-

dominantly a product of the fundus portion of the stomach. Hence, we assumed that the failure to demonstrate antipernicious anemia effectiveness in fundus tissues could be attributed to their pepsin content. To test this hypothesis the three cases here reported were treated with depepsinized whole stomach mucosa and depepsinized fundus and pylorus mucosa, obtained from the hog's stomach under proper conditions for preserving antipernicious anemia potency according to Greenspon. The treatment of the patients was checked in such a fashion that significant results were obtained. In considering these results the attempt was made to evaluate the relative rôles of intrinsic factor, extrinsic factor and intestinal permeability. The absorptive ability of the intestinal mucosa is a rather uncertain factor in cases of pernicious anemia since it is not altogether unlikely that the morbid process underlying the disease also produces impairment of cell permeability. Perhaps this is one reason for the greater potency of intramuscular preparations.

Conclusions

1. The feeding of depepsinized whole stomach mucosa, "Mucex," with and without the addition of extrinsic factor, was not significantly effective in pernicious anemia.

2. The feeding of depepsinized fundus mucosa with and without the addition of extrinsic factor, was not effective in pernicious anemia.

3. The feeding of depepsinized pyloric mucosa without the addition of extrinsic factor was not effective. However, when extrinsic factor was added there was a minimal, though definite, evidence of antipernicious anemia activity.

4. Intestinal permeability is often impaired as is shown by the submaximal responses to the administration of oral preparations of known activity.

5. The claim for higher activation by depepsinization by Greenspon has not been sustained. His conception of the existence of an antipernicious anemia principle, excluding the action of the extrinsic factor, has not been confirmed.

6. The possibility of completely depepsinizing fundus tissues by present methods is debatable. Perhaps this explains the complete inactivity of fundus preparations.

7. The suggestion is made that the process of depepsinization may not always result in the same end-product. In one instance an active product may be obtained, in another an inactive one. Therefore, the investigations here reported only suggest a refutation of Greenspon's findings.

8. Unless disproved, Greenspon's demonstration of the antagonism of pepsin toward the antipernicious anemia factor (Castle's intrinsic factor) considered along with the known adsorptive capacity of protein for pepsin and coupled with the histological knowledge of peptic cell predominance in the fundus of the stomach suggests a rôle for the fundus in pernicious anemia. This is now under investigation.

REFERENCES

1. Greenspon, E. A.: The nature of the antipernicious anemia principle in stomach, Jr. Am. Med. Assoc., 1936, cvi, 266.
2. Meulengracht, E.: The glands of the stomach in relation to pernicious anemia; with special reference to the glands in the pyloric region, Proc. Roy. Soc. Med., 1935, xxviii, 37.
3. Ungley, C. C., and Moffett, R.: Observations on Castle's intrinsic factor in pernicious anemia, Lancet, 1936, ccxxx, 1232.
4. Hanes, F. M., Hansen-Prüss, O. C., and Edwards, S. W.: The feeding of modified gastric juice in pernicious anemia, Jr. Am. Med. Assoc., 1936, cvi, 2058.
5. Fitz-Hugh, T., Jr., and Creskoff, A. S.: Experiments with "depepsinized" human gastric juice in the treatment of pernicious anemia, Am. Jr. Med. Sci., 1936, cxcii, 168.
6. Castle, W. B., and Ham, T. H.: Observations on the etiologic relationship of achylia gastrica to pernicious anemia, Jr. Am. Med. Assoc., 1936, cvii, 1456.
7. Lim, R. K. S.: A method for recording gastric secretion in acute experiments on normal animals, Quart. Jr. Exper. Physiol., 1922–23, xiii, 71. The question of a gastric hormone, Quart. Jr. Exper. Physiol., 1922–23, xiii, 79.
8. Henning, N., and Brugsch, H.: Ueber die Verteilung des antianämischen Faktors in der Magenschleimhaut, Deutsch. med. Wchnschr., 1931, lvii, 757.
9. Gutzeit, K., and Herrmann, J.: The effect of stomach substance on pernicious anemia (natural gastric juice, pyloric and fundic mucosa, wall of the small intestine), München. med. Wchnschr., 1931, lxxviii, 266.
10. Henning, N., and Stieger, G.: Die Behandlung der perniziösen Anämie mit Magenschleimhautpräparaten, Klin. Wchnschr., 1930, ix, 2145.
11. Henning, N.: Ueber den Ursprung des Antiperniziosa-Prinzips, Med. Welt, 1934, viii, 1145.

THE PATHOGENESIS OF BANTI'S DISEASE*

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In 1883 Banti wrote a monograph entitled "dell Anemia Splenica." In this monograph he described a group of cases presenting splenomegaly with anemia and leukopenia. A particular and, to him, pathognomonic histologic change appeared in the spleen and he insisted that the disease resulted from the activities of some unknown toxic agent that irritated first the spleen and secondarily the liver.

In the next 10 years 10 more papers were written by Banti on this syndrome; his name became firmly attached and the syndrome entered the medical texts as Banti's disease.

In this country Osler published several papers—the first in 1900—on this disease picture. The clinical pattern, as defined by him, remains as the standard definition in subsequent textbooks of medicine.

This definition of Banti's disease, or splenic anemia, reads as follows: "An intoxication of unknown nature characterized by great chronicity. There is a primary progressive enlargement of the spleen which cannot be correlated with any known cause, anemia of the secondary type with leukopenia—a marked tendency to hemorrhage from the lower oesophagus and a terminal state with cirrhosis of the liver."

The members of the Spleen Clinic at the Presbyterian Hospital have, for the past 10 years, been particularly interested in this syndrome. During these years we have had the unusual opportunity of observing 137 cases of this general type. Of this total group 100 have been followed for a sufficient number of years, under circumstances that are nearly ideal for clinical investigation.[1] Splenectomies have been done in 68 instances. As a result of this 10 year study, our view of this condition has altered. A concept of the pathogenesis of the syndrome has developed which is different from that generally accepted and is presented here for the first time.

Early in our study it became necessary to agree upon the criteria by which patients could be placed into this clinical group. These criteria can be stated as follows: Splenomegaly with anemia, leukopenia and thrombocytopenia with evidence of the development of increased collateral circulation between the portal and peripheral venous circulation and histologic changes in the spleen that are characteristic.

The first intimation that the accepted concept should be questioned occurred early in our studies with the appearance of a patient, E. W., Unit No. 318773. This patient was a young, healthy, vigorous policeman who in 1928 suffered an epigastric injury as a result of accident. The injury was

* Read at the Cleveland meeting of the American College of Physicians April 2, 1940.
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followed by the appearance of a traumatic pancreatic cyst which was removed. At the time of this operation his spleen was not enlarged and his blood count was normal. After this operation, he developed, over a period of three years, a slowly progressive splenomegaly with falling peripheral blood values until 1931 when the clinical diagnosis of Banti's disease was fully apparent. Splenectomy by Dr. Whipple on June 2, 1932, showed a very large spleen with dilated, tortuous portal vessels. The splenic vein entered the scar of the pancreatic operation at which point the blood flow in the vein was seriously impeded by a constricting band of dense connective tissue. The liver appeared normal. The patient made an uneventful recovery, his blood values promptly returned to normal and he has been without symptoms for eight years. His blood is normal, and there has been no clinical evidence of liver disease. It was obvious to all of us who followed this patient that we were dealing with a purely mechanical situation that had resulted in a clinical and histological picture indistinguishable from the Banti syndrome. Because of the presence of such an obvious mechanical factor in this case, and because of the gross appearance of the portal system at operation in other cases, we began to wonder if obstruction to the flow of splenic vein blood might not be an important element in the production of this syndrome. The promptness with which the splenomegaly may vanish after hematemesis was further evidence of venous tension, and as new cases came to operation we noticed a variety of different lesions associated with this syndrome. Some of these lesions were intrahepatic, others were extrahepatic, but all could produce splenic vein hypertension.

The possibility that chronic splenomegaly might result from some interference with the flow of portal blood has been mentioned by several authors. Eppinger [2] and Warthin [3] both suggested that at least in some cases of splenic anemia a mechanical factor appeared to exist. McMichael [4] refers to the importance of portal hypertension in some cases of splenomegaly and he and McNee [5] both discuss the possible importance of this factor in the production of Banti's disease. But nowhere in these papers can one find a definite statement presenting this factor as the actual cause of this clinical picture.

The results of our studies on the splenic vein pressure levels in this syndrome have been published.[6] When compared with the venous pressure in the peripheral circulation or with the splenic vein pressures in other types of splenomegaly there is no doubt but that splenic vein hypertension, of great magnitude, is an important and invariably present factor in this disturbance. Table 1 shows these readings.

In 1936 and 1939 [7,8] Rousselot reported on the importance of this mechanical factor in our earlier cases. He stated the tentative views of the Spleen Clinic group on the pathogenesis of the syndrome at that time. Further study of an increasingly large number of cases has tended to extend and clarify this idea.

It is our current concept that Banti's disease, or splenic anemia, is the result of mechanical obstruction to the flow of blood within the portal system.

TABLE I

Venous Pressures in Millimeters of Normal Saline

Banti—*Laennec Cirrhosis*

Pt.	Splenic Vein	Arm Vein
C. M.	225	12
C. M.	325	85
D. P.	450	125
N. A.	470	145
R. B.	370	30
S. S.	360	150
G. A.	260	190

Banti—*Thrombosis of Splenic Vein*

Pt.	Splenic Vein	Arm Vein
J. S.	390	170

Banti—*Schistosomiasis Mansoni*

Pt.	Splenic Vein	Arm Vein
P. R.	250	50
A. E.	335	105
G. P.	500+	70
C. C.	415	125
L. M.	375	60
H. B.	377	110

Banti—*Obstructive Factor Undetermined*

Pt.	Splenic Vein	Arm Vein
L. D.	275	105
C. K.	370	50
B. S.	330	55
P. M.	465	110

Controls

Pt.	Splenic Vein	Arm Vein	Diagnosis
F. H.	190	65	Lymphosarcoma
R. B.	105	80	Hemolytic jaundice
L. L.	220	205	Atypical hemolytic jaundice
N. B.	125	130	Hemolytic jaundice
S. S.	215	40	(shock) Gaucher's
L. L.	190	107	Splenomegaly of undetermined origin
W. U.	120	95	Hemolytic jaundice
S. J.	360	−5	(severe shock) Purpura
Z. G.	185	75	(beginning shock) Pancreatic adenoma
S. L.	190	210	Purpura
G. C.	235	165	Splenomegaly of undetermined origin
E. N.	275	205	Atypical hemolytic jaundice
T. K.	70	300	Purpura
M. M.	140	65	Purpura
J. K.	245	240	Lymphatic leukemia
A. M.	175	125	Splenomegaly of undetermined origin
J. B.	225	185	Hemolytic jaundice
H. A.	180	20	(in shock) Reticulo-endotheliosis
H. R.	290	290	Giant foll. hyperplasia
S. R.	180	165	Hemolytic jaundice

The site and character of the obstruction must be such that a chronic increase in splenic vein pressure will occur. At the same time the venous pressure in the peripheral circuit should be approximately normal. This differential in heads of pressure is, we believe, the actual cause of the splenomegaly and

explains the collateral circulation. With high portal pressure and relatively low peripheral venous pressure, a reversal in the direction of normal blood flow can take place in at least part of the portal system. This reversal in direction of blood flow is the direct result of the abnormal hemodynamics that exist in these cases and is permitted to occur by the absence of valves in the portal system.

A careful review of our clinical material leads to the conclusion that there are no significant differences, clinical or hematological, between the congestive splenomegalies resulting from the various obstructive factors. Variations may occur in the velocity of progress, depending upon the nature of the underlying disturbance, but the basic disease pattern is the same in all of our subdivisions.

Of equal importance is the fact that the splenic histology is the same in all groups. A recent review of the microscopic sections of 68 spleens of patients with congestive splenomegaly has led Dr. H. D. Kesten, of the Department of Pathology, and myself to the conclusion that no detectable histologic differences exist between the spleens of the various subdivisions of this syndrome. All show variable degrees of follicular atrophy; all present fibrosis of the pulp with dilated venous sinuses; all have the very characteristic perifollicular hemorrhages. The presence of siderotic nodules would seem to depend largely upon the accidental inclusion of one or more in any given section.

The obstructive lesions that are responsible for this secondary congestive splenomegaly are divisible into two main groups: intrahepatic and extrahepatic.

The intrahepatic lesion responsible for congestive splenomegaly is cirrhosis. Of our total group, hepatic cirrhosis was present as the obstructive factor in 68 per cent.

Scarring of the liver causes increased portal pressure in two ways. First, there is an increased resistance to the flow of portal blood through the liver caused by the constricting bands of periportal connective tissue. Second, there is a distortion of the normal hepatic artery—portal vein anastomoses—that permits the transmission of arteriolar pressures to portal vein radicals.

The double mechanism has been carefully studied by others. Perfusion experiments in normal and cirrhotic livers [9] and histologic studies of the intrahepatic vascular bed [10] in normal and scarred organs show that this conclusion may be accepted.

Of chief concern to us is the question of the relation between the type of hepatic scarring and the degree of portal hypertension. Cirrhosis, in general, tends to be associated with splenomegaly of the congestive type. The amount of splenomegaly, however, is variable and it is important to try to determine what types of cirrhosis result in Banti's disease and what types do not.

We have studied this question from various angles, with the assistance

of qualified pathologists and clinicians. Our current conclusions may be summarized as follows:

(1) The type of hepatic scarring seen in prolonged schistosomiasis results in the greatest increase in portal pressures and the largest spleens. The behavior of this parasitic disease is ideal for the production of portal hypertension. The adult worms reside in the pelvic and perirectal radicals of the portal system. The large spiked ova drift with the blood flow into the smaller intrahepatic portal vessels where they lodge, disintegrate, and set up the typical " pipe stem " type of scarring. The ova do not reach the spleen, in our experience, except in massive infestations. This slowly progressive distortion of the intrahepatic radicals of the portal vein results in a slowly rising portal vein pressure. Secondary to this portal hypertension there develops the typical clinical and pathological picture of Banti's disease and it is this sequence that is responsible for much of the splenic enlargement seen in Egypt,[11] China [12] and the Caribbean area.[13]

A similar sequence of events has been produced experimentally by Rousselot and myself [14] by injecting silica particles into the splenic veins of dogs. Here again, the slowly progressive periportal scarring produces rising portal pressures and results, after two years, in congestive splenomegaly with extensive collateral circulation.

(2) In our experience, biliary cirrhosis and cardiac cirrhosis do not produce congestive splenomegaly. Very rarely, prolonged cardiac decompensation may produce unusually dense hepatic scars with resultant portal hypertension and mild splenomegaly of the Banti type.

(3) Periportal cirrhosis of the Laennec type results in a variable degree of splenomegaly. A recent review of 81 autopsied cases reveals certain interesting and important correlations between the type of hepatic scarring and the amount of portal hypertension. Approximately 60 per cent of the 81 cases recorded as Laennec cirrhosis in the files of the Department of Pathology have an associated splenomegaly of the Banti type and esophageal varices. In this 60 per cent the periportal scars are dense, there is great distortion of the intrahepatic vascular bed, and there is minimal evidence of liver cell damage. Many of these patients present the clinical features of Banti's disease and many ultimately die of hemorrhage from rupture of the esophageal varices. In the remaining 40 per cent there is less connective tissue, less distortion of the vascular bed, and more evidence of injury of the liver parenchyma, and these individuals die of hepatic insufficiency with clinical cholemia. Intermediate stages between these two types exist, but we feel we can predict, with considerable assurance, the degree of splenomegaly in any case from examination of the microscopic section of the liver. It is wise to remember that the important lesion is in the liver and that the extent, type, and velocity of progress of the liver lesion is what determines the prognosis of the patient's disease.

One other statement that can be made with respect to this whole group

of congestive splenomegalies secondary to hepatic scarring is that when cirrhosis, if looked for, does not exist as the obstructive agent at the time of splenectomy, it will not appear subsequently. We have yet to see a patient develop the sequence of events characterized by Banti as the three stages of this syndrome. Cirrhosis exists in over half of our cases as the obstructive factor; in the remainder the obstruction to the portal flow lies elsewhere and evidence of cirrhosis does not appear even after years of careful clinical study or at subsequent autopsy.

The extrahepatic lesions responsible for congestive splenomegaly are many and varied. Thrombosis of the portal or splenic veins may occur as a result of injury or infection and we have several examples of Banti's disease, typical in all respects, resulting from this obstructive lesion.

The peculiar lesion known as cavernomatous transformation of the portal vein, with or without an underlying thrombosis, has been present as the obstructive mechanism in two cases. Compression of the splenic vein by tumors and scars is a rare cause of this syndrome. And we have been interested recently in a group of 30 patients who have developed the Banti syndrome during childhood. In about 50 per cent of this younger age group, Laennec's cirrhosis of the liver has been present as the obstructive mechanism. In others a definite obstructive factor has not been found at operation and most of these patients ultimately have died of hematemesis. As several of these juvenile patients developed evidences of congestive splenomegaly before the age of one year, we have wondered if the obstructive mechanism might not be a defect in the portal vein, either an anatomical developmental defect or a thrombosis occurring at the time of birth coincident with the thrombosis of the umbilical vein, as a result of this normal process extending beyond its usual limits.

As only four of this younger extrahepatic group have come to autopsy we cannot be absolutely sure of the obstructive mechanism in all. But in these four a stenosis of the portal vein was found as the cause of the portal hypertension. The site of the stenosis and its apparent duration suggest that it occurred either shortly before or just after birth. Rousselot, in a recent report to the Society of University Surgeons, states that he believes that this lesion is responsible for the non-cirrhotic group of Banti's syndrome that occurs in infancy and childhood. It is an interesting lesion and deserves further study.

Certain statements can be made with respect to this whole group of cases:

1. Direct or indirect evidence of portal vein hypertension exists as the common denominator in all cases of so-called Banti's disease or splenic anemia.

2. This portal hypertension in the presence of normal peripheral venous pressure results in the splenomegaly, the collateral circulation, and the esophageal varices.

3. A simple mechanical reason for this hypertension can be found in every case that can be adequately studied.

4. Hepatic cirrhosis exists in 68 per cent of our series as the obstructive factor. When cirrhosis is not present at the time of splenectomy it will not appear subsequently.

5. No clinical or hematological differences can be found between patients with congestive splenomegaly due to intra- or extrahepatic obstructions, except in cases of advanced liver disease when the clinical features of hepatic insufficiency will appear and assume preponderance.

6. The splenic histopathology is the same in all cases of congestive splenomegaly—it is similar in type to the changes described by Banti and others—there are no visible differences in the various groups.

It is, therefore, our present contention that Banti's disease or splenic anemia is a secondary mechanical manifestation of any of a variety of lesions producing a chronic splenic vein hypertension. We consider this syndrome as a mechanical congestive splenomegaly, a term suggested by Larrabee.[15]

In any given case the prognosis, with or without splenectomy, depends upon the nature and the location of the obstructive mechanism. In the extrahepatic group the cause of death is hemorrhage from ruptured esophageal varices. The majority of the intrahepatic group die of liver insufficiency, except in the pure periportal schistosomiasis cases, where death is from hemorrhage.

It is our experience and the experience of others that splenectomy is usually followed by a return of the blood values to normal. The threat of lethal hematemesis continues to be present in spite of splenectomy in those cases where the obstructive factor lies within the liver or in the portal vein. Splenectomy has no visible effect upon the progress of cirrhosis. But splenectomy should and, in our experience, does definitely cure that unfortunately small group where the splenic vein alone is involved.

Conclusions

1. Banti's disease or splenic anemia results from a variety of primary lesions that produce splenic vein hypertension.

2. We believe that this syndrome is a secondary, mechanical congestive splenomegaly and we can find no reason for assuming the presence of an unknown toxic agent.

3. There is no justification for retaining the concept of three stages in development. In our experience cirrhosis of the liver exists only as one of the several obstructive mechanisms; if it is not present as the obstructive mechanism at the time of splenectomy, it will not develop subsequently.

4. We suggest that the terms Banti's disease and splenic anemia be replaced by congestive splenomegaly.

BIBLIOGRAPHY

1. WHIPPLE, ALLEN O.: The medical-surgical splenopathies, Bull. New York Acad. Med., 1939, xv, 174.
2. EPPINGER, H.: Die Hepato-lienal Erkrankungen, 1920, Springer, Berlin.
3. WARTHIN, A. S.: Relation of thrombophlebitis of the portal and splenic veins to splenic anemia and Banti's disease, Internat. Clin., 1910, iv, 189.
4. MCMICHAEL, J.: Pathology of hepatolienal fibrosis, Jr. Path. and Bact., 1934, xxxix, 481.
5. MCNEE, J. W.: The spleen (Lettsonian Lectures), Lancet, 1931, i, 951, 1009, 1063.
6. THOMPSON, W. P., CAUGHEY, J. L., WHIPPLE, A. O., and ROUSSELOT, L. M.: Splenic vein pressure in congestive splenomegaly (Banti's disease), Jr. Clin. Invest., 1937, xvi, 571.
7. ROUSSELOT, L. M.: The rôle of congestion (portal hypertension) in so-called Banti's syndrome, Jr. Am. Med. Assoc., 1936, cvii, 1788.
8. ROUSSELOT, L. M.: Congestive splenomegaly, Bull. New York Acad. Med., 1939, xv, 188.
9. HERRICK, F. C.: An experimental study into the cause of increased portal pressure in portal cirrhosis, Jr. Exper. Med., 1907, ix, 93.
10. JOHNSTON, J. M.: The relation of changes in the portal circulation to splenomegaly of the Banti type, ANN. INT. MED., 1931, iv, 772.

11a. DAY, H. B.: Bilharzial cirrhosis and Egyptian splenomegaly, Jr. Trop. Med., 1933, xxxvi, 17.

11b. MOHAMED, A. S.: Historical review of Egyptian splenomegaly, Jr. Egyptian Med. Assoc., 1936, xix, 631.

12. CAMPBELL, H. E.: Schistosomiasis and Banti's disease, Chinese Med. Jr., 1936, l, 1561 and 1938, liii, 459.
13. BONELLI, P.: Analogia entre la Schistosomiasis Mansoni y la enfermedad de Banti o Anemia esplenica, Bol. Asoc. Med. de Puerto Rico, 1931, xxiii, 251.
14. ROUSSELOT, L. M., and THOMPSON, W. P.: Experimental production of congestive splenomegaly, Proc. Soc. Exper. Biol. and Med., 1939, xl, 705.
15. LARRABEE, R. C.: Chronic congestive splenomegaly and its relation to Banti's disease, Am. Jr. Med. Sci., 1934, clxxx, 745.

CLINICAL OBSERVATIONS ON BLOOD IRON *

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THREE years ago at the Robert Dawson Evans Memorial, one of us (B. S. W.) adapted for determination of iron in whole blood the Wong [1] method using the photoelectric colorimeter of Evelyn.[2] Since then we have used this method almost as a routine in studying cases admitted to the hospital.

The following procedure is used: into a 100 c.c. volumetric flask the following are successively pipetted:

1 c.c. blood
4 c.c. concentrated sulfuric acid
4 c.c. saturated aqueous solution of potassium persulfate.

The mixture is shaken and allowed to cool. Distilled water is added until the flask is approximately half full, then 4 c.c. of 10 per cent aqueous solution of sodium tungstate, and finally distilled water to the 100 c.c. mark. After mixing and filtration, to 20 c.c. of the clear filtrate is added 1 c.c. of the persulfate solution and 4 c.c. of 3N potassium thiocyanate solution to which have been added 40 c.c. of acetone per liter of solution. This treatment of the filtrate with persulfate and thiocyanate is carried out in an Evelyn tube, the colorimetric reading being made promptly in the Evelyn instrument. The filter used transmits light at a wave length of 490 mu; the maximal absorption of a solution of ferric thiocyanate is at a wave length of 480 mu. Calculations are made from a curve obtained by actual determinations of galvanometer deflection with known iron solutions, or by the equation

$$\text{Mg. Fe per 100 c.c. blood} = \frac{(2\text{-Log } G) \times 100}{K},$$

where G is the galvanometer deflection and K has the experimentally determined value of 2.44.

Up to July 13, 1939 the concentration of iron was determined in 2608 different samples of blood. When the data from these analyses were assembled, the blood-iron concentrations formed a frequency curve, the commonest blood-iron level being around 47, with a range between 8 and 86 mg. per 100 c.c.

To the best of our knowledge, this is the first tabulation of such a large series of blood-iron determinations. From so simple a statistical analysis it appears that by this method, and in this particular series, bloods containing less than 31 mg. of iron per 100 c.c. were unquestionably abnormal just as were bloods which contained more than 55 mg. per 100 c.c. As a whole, bloods with an iron concentration of less than 47 mg. per 100 c.c. were more

* Read at the Cleveland meeting of the American College of Physicians, April 4, 1940.
From the Robert Dawson Evans Memorial for Clinical Research and Preventive Medicine, the Massachusetts Memorial Hospitals, Boston.

frequently encountered than were bloods with an iron level above this figure. In other words, a slight or moderate degree of blood-iron deficiency was more commonly found than a corresponding degree of iron plethora.

The value of 47 mg. per 100 c.c., although the mode of this series, should not be considered as a strictly normal average blood-iron value. The pa-

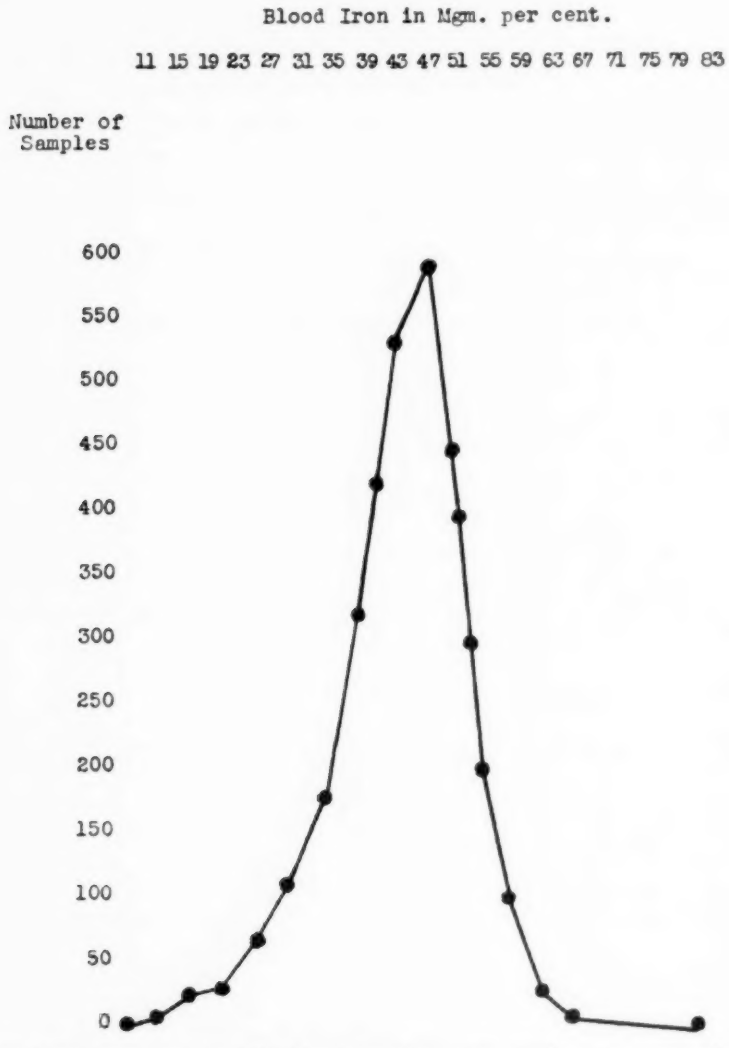

FIG. 1. The blood-iron level in 2608 blood samples. The readings for convenience have been grouped in successive steps of 4 mg. per 100 c.c. of blood.

tients in this series were not normal but were sufficiently ill to warrant admission to a hospital. A study of normal subjects by Sachs, Levine and Fabian [3] has established the normal blood-iron level for males at about 50 mg. per 100 c.c., and for females at about 43.5 mg.

There were among the definitely abnormal bloods 257 samples (10 per cent of the series) which contained less than 31 mg. of iron per 100 c.c., and 138 samples (5 per cent of the series) which contained more than 55 mg. The iron-poor blood samples were obtained from 64 different cases and the iron-rich samples from 75 different cases. We determined to study the individual records of these cases in order to discover what circumstances are likely to lead to a significantly abnormal blood-iron level and whether information obtained from the blood-iron level is of any definite clinical interest.

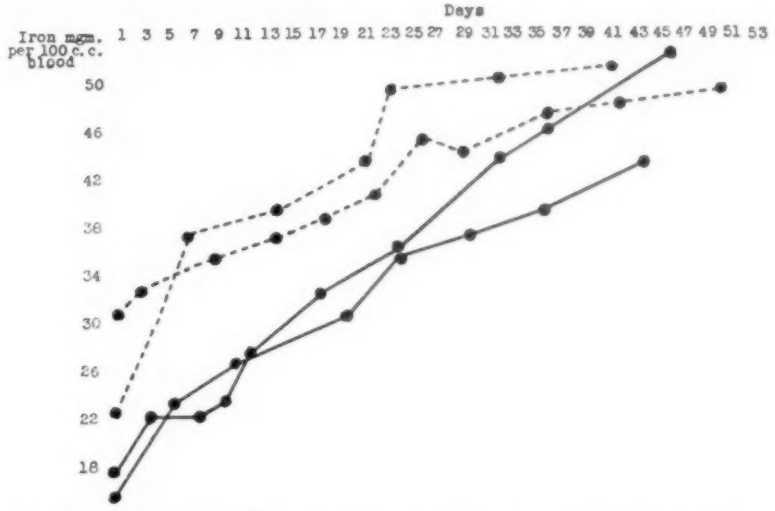

FIG. 2. The blood-iron level in two cases of pernicious anemia under treatment with liver and without iron, and in two cases of simple secondary anemia under treatment with iron and without liver. The pernicious anemia blood-iron curves are dotted. The secondary anemia blood-iron curves are solid.

Before considering any of the cases in detail, it may be well to recapitulate the present state of knowledge as to the forms of iron present in the blood and their distribution. Nearly all of the iron of the blood is in the red cells: plasma or serum contains normally about 0.1 mg. of iron per 100 c.c.,[4] or about 0.2 per cent of the total iron of the blood. In certain types of anemia [4] or following intensive iron therapy [5] the plasma or serum iron may be increased to several times this value. Considering both the possibility of an elevation of the serum iron and a depression of the total iron of the blood in anemias, the percentage of the total iron assignable to the plasma can in all reasonable probability surely never exceed 5 per cent. This leaves 95 per cent or more (usually 99 per cent or more) of the total iron of the blood to be accounted for in the corpuscles. The major portion of this iron is in the form of hemoglobin; a minor portion (not more than 10 per cent at the most, usually less than 5 per cent of the total iron) is present in the form of degradation products of hemoglobin in which the iron and globin are still in union with an *opened* porphyrin ring . . . the "pseudohemoglobins" of

Barkan and Schales,[6] previously designated by Barkan [7] as "leicht abspaltbares Bluteisen." The greatest single factor, then, influencing the total iron of the blood is the amount of hemoglobin present, accounting for 85 to 95 per cent (usually the latter) of the total iron. In a rough fashion the interpretation of blood-iron values is comparable to the interpretation of hemoglobin values; exact agreement is not obtained on account of the presence of varying amounts of non-hemoglobin iron, even when the method used for the measurement of hemoglobin is comparable in accuracy with that used for iron, as in the work reported by Klumpp.[8] The customary methods for the

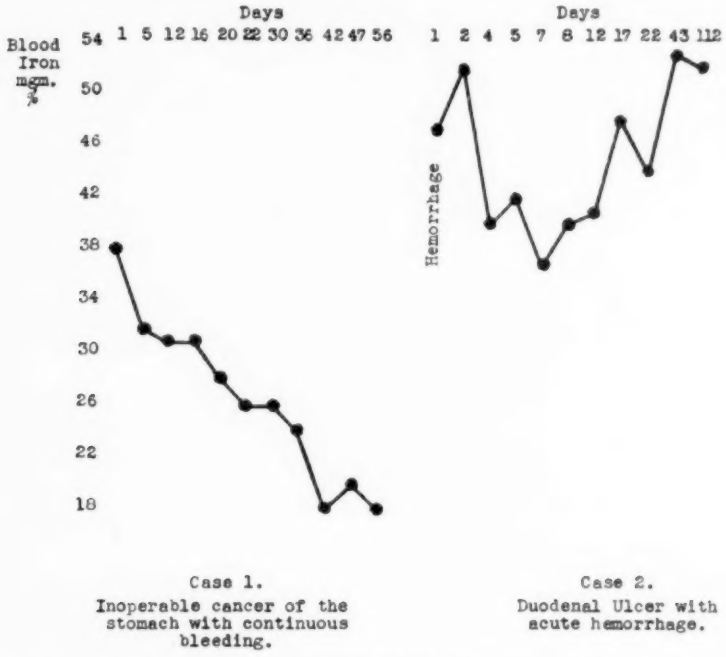

FIG. 3. The blood-iron level as affected by continuous bleeding and by acute hemorrhage.

measurement of hemoglobin in clinical laboratories are for the most part based upon the measurement of the color of acid hematin. Such methods are fundamentally inaccurate and subject to frequent inexplicable fluctuations as shown by Barkan [9] and others. The measurement of the total iron of the blood can be made, by the method described above or by several other methods, with analytical precision.

To return to our own cases. In the iron-poor group were examples of nearly all the clear-cut, well-established causes for depletion of hemoglobin. These included hemorrhage, pernicious anemia, myelophthisic anemia, aplasia of the bone marrow resulting from so-called idiopathic aplastic anemia, aplastic anemia following radiation in one patient who appeared hypersensitive to that form of therapy, and finally depletion of blood-iron and aplasia

of the marrow secondary to long-standing chronic infections or to chronic intoxication as occurs in cancer, advanced liver disease, or in chronic nephritis, particularly in chronic pyelonephritis. Hemorrhage, either acute or chronic, was the commonest single cause of an abnormally low blood-iron level.

Certain facts in these cases were outstanding. Too low a blood-iron level, for example, was an ominous sign. Of twelve cases in which the blood-iron level reached a point below 20 mg. per 100 c.c., nine died in a comparatively short time in spite of repeated transfusions or varying combinations of transfusions and liver or iron therapy.

The almost mathematical precision and parallel manner in which the level of blood-iron increased under appropriate treatment in cases with pernicious anemia receiving liver or in cases of anemia from hemorrhage receiving an adequate supply of iron was striking.

On the whole, the blood-iron level tended to be relatively high in severe pernicious anemia before treatment in contrast to its low level in severe un-

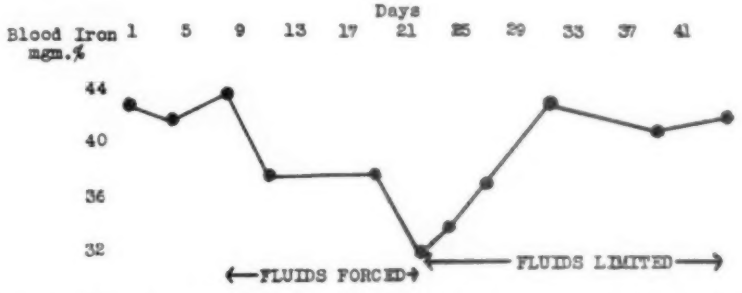

FIG. 4. The blood-iron level as affected by dilution from fluid retention.

treated hypochromic anemia. It often was easier to establish blood-iron levels higher than normal in pernicious anemia without the administration of iron than normal blood-iron levels in hypochromic anemia even with very high iron dosage. Obviously there is a striking difference between the iron metabolism of pernicious anemia on the one hand and that of hypochromic anemia on the other. In one condition iron is present in the body but cannot be used because of ineffective red corpuscle formation, and in the other iron is lacking or not usable in the body although normal iron carriers are available.

The response of the blood-iron to hemorrhage may be varied. We have noticed that following an acute, not excessive, intestinal hemorrhage there may at first appear an elevation in the blood-iron level followed later by a fall: whereas in persistent continuous loss of blood there is apt to be a steady decrease in blood-iron concentration. (Figure 3.)

In Case 1 there was continuous loss of blood each day and therefore a steady drain on the iron reserve with resultant depletion of stored iron. In Case 2 there was at first concentration of blood resulting from a sudden

hemorrhage followed later by blood dilution and iron loss through bleeding, with final re-establishment of normal values. (Figure 4.)

One patient well illustrated the changes in blood-iron level which may occur from dilution of blood alone. The patient, a young man, was a diabetic. He developed an abscess of the lung following extraction of a

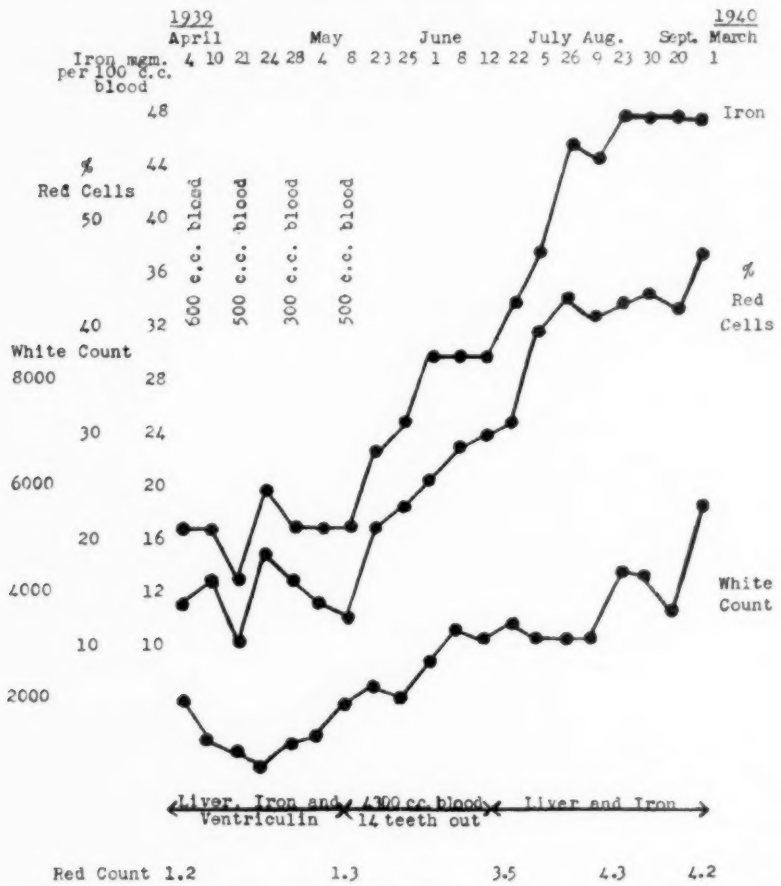

FIG. 5. The blood-iron level, the hematocrit reading, the white count and red count in a case of atypical anemia.

tooth and for this reason entered the Hospital. During the acute stage of this complication he received by vein large amounts of fluid. At first we did not realize how much fluid was being retained under such treatment and we were well on our way toward inducing a marked edema. Later by restricting the fluid intake a diuresis occurred with reconcentration of the blood. The various phases of dilution and concentration of the blood were well reflected by the blood-iron level.

It has been repeatedly emphasized that if the carriers of iron—the red discs—are at fault as in pernicious or aplastic anemia, treatment with iron

at least at first, is not necessary or helpful. On the other hand, if the storage of iron in the body is depleted, iron in some form is chiefly required and devices to improve the transportation of iron are unlikely to be very helpful. It is probable that certain cases of anemia result from a two-fold mechanism due to a combination of depleted iron stores and faulty iron transportation. A patient with an atypical anemia associated with splenomegaly, leukopenia and a tendency to bleeding gums perhaps fell into this category.

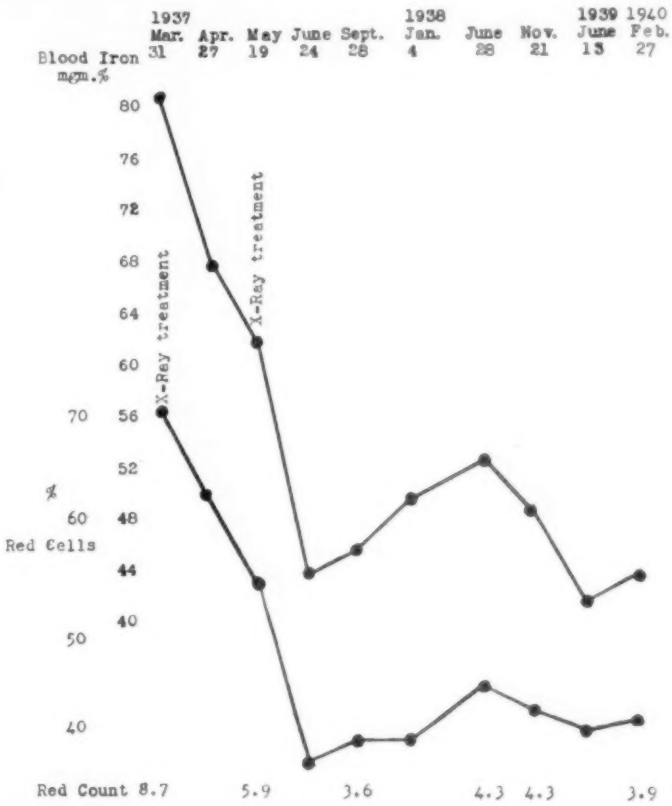

FIG. 6. The blood-iron level, the hematocrit reading and the red count in a case of polycythemia vera treated by radiation.

At first liver, stomach and iron therapy were without demonstrable effect. It was thought that the patient had aplastic anemia. Multiple transfusions were then given, 500 c.c. every three days for several weeks. During this period several badly infected teeth were removed. Finally the patient was given a diet high in vitamins, supplemented by liver and iron. Now there developed a slight reticulocytosis (3 per cent) which had not been heretofore obtained and steady improvement. (Figure 5.)

Apparently this patient had depleted iron storage: our reason for believing this was the low blood-iron level first encountered which was lower than

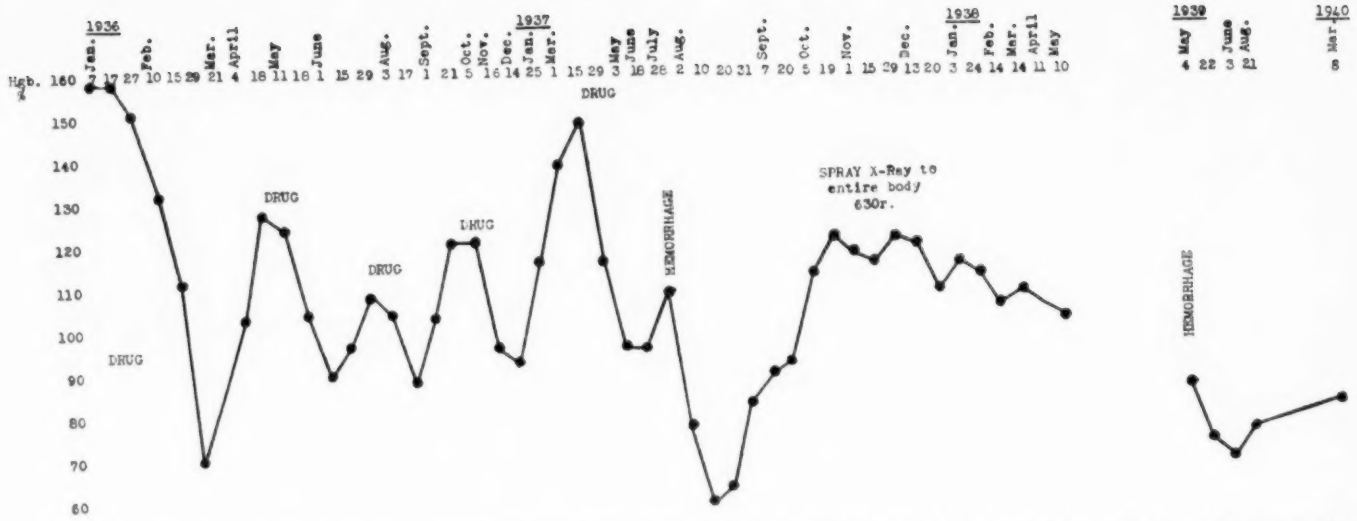

FIG. 7. The hemoglobin level in a case of polycythemia vera treated by acetylphenylhydrazin, and by radiation, and complicated by spontaneous hemorrhage. Hemoglobin values have been substituted for blood-iron figures as the latter were not available for the entire period.

is usual in pernicious anemia. In addition to persistent bleeding, another factor in depleting the iron storage may have been a diminution of hydrochloric acid in the gastric juice and therefore she may have absorbed iron with difficulty. And finally, possibly as a result of infection, the bone mar-

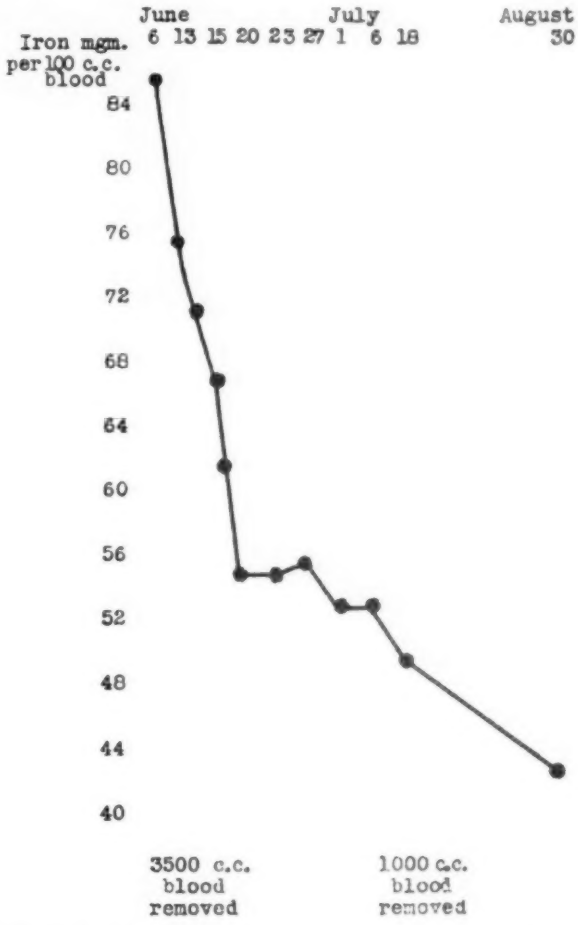

FIG. 8. The blood-iron level in a case of polycythemia vera treated by copious bleeding.

row had become relatively aplastic and therefore the iron transport was abnormal.

Transfusion supplied iron, for normal blood appears to afford the most satisfactory method at present available for the parenteral administration of iron. Five liters of blood, containing (approximately) 470 mg. of iron per liter, supplied in a short time more than 2 grams of iron. The removal of infected teeth did away with a possible cause of bone marrow aplasia. When the iron storage approached adequacy and the marrow was no longer aplastic, improvement became possible. We are by no means certain that our ex-

planation of this case is correct, nor that the results of our treatment will be lasting. The explanation given is at least not altogether unreasonable.

Theoretically, significant degrees of anemia could develop in the presence of adequate iron storage and of normal facilities for iron transport if, through some form of abnormal metabolism, iron might not be made into hemoglobin at a normal rate. We have encountered a few cases of anemia in myxedema, for example, which did not initially respond to iron or liver or both. The anemia gradually corrected itself, sometimes without any accessory treatment, when the basal metabolic rate was maintained at a normal level over a long period of time by thyroid administration. It seems possible that faulty oxidation processes may have made the iron stores unavailable for hemoglobin synthesis. The effect of thyroid administration in stimulat-

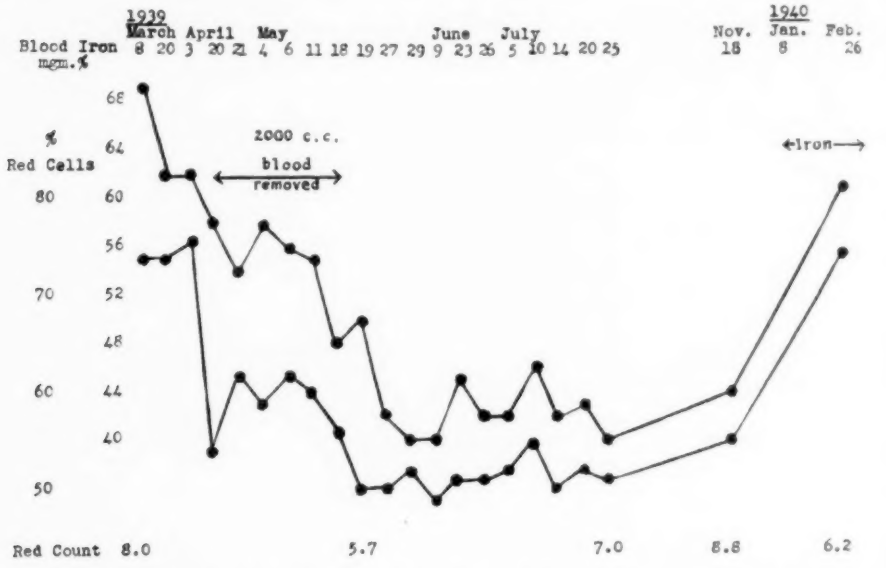

FIG. 9. The blood-iron level, the hematocrit reading and the red count in a case of secondary polycythemia treated by bleeding, and later by iron.

ing the formation of red discs even in non-myxedemic subjects has been reported by Hoskins and Sleeper.[10]

In light of these considerations we believe that a knowledge of the blood-iron level, in addition to its obvious function of serving as a check on hemoglobin estimations, affords information of definite value in the diagnosis and treatment of the several forms of anemia. It directs the attention of the clinician to the general state of the patient's iron metabolism, a matter which in the management of the anemias is not only of theoretical interest, but of very practical importance.

Certain of the patients with too high a level of blood-iron proved equally interesting. There were in the group four cases of polycythemia vera. Of these, three have been followed for a sufficiently long time to be worth dis-

cussing from the viewpoint of iron metabolism, particularly because each one has been treated in different fashion.

The first patient, a man of 55, developed polycythemia in 1935. He had all the earmarks of the disease including an excessively high hemoglobin concentration, a red count of more than eight million and a palpable spleen. At first he was given large doses of Fowler's solution with subjective benefit. But the drug, to be effective, had to be given in uncomfortably large quantity so that in 1937 a more radical treatment was attempted. He was given two courses of roentgen-ray treatment by Dr. George W. Holmes at the Massachusetts General Hospital. Observations on the blood-iron level have been made from time to time since then with the results shown in figure 6.

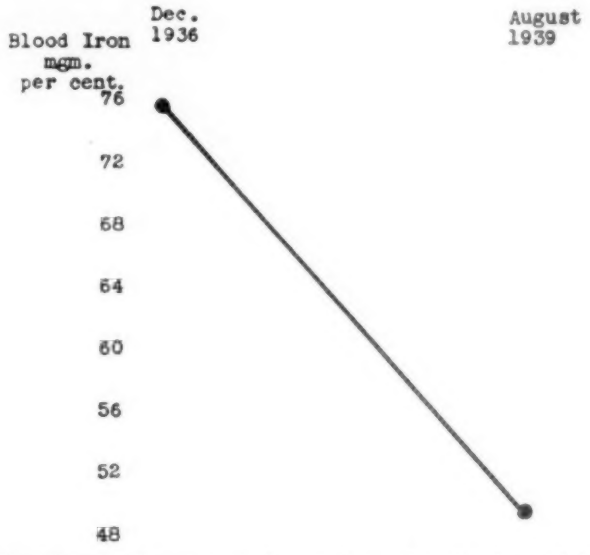

FIG. 10. The blood-iron level in a case of secondary polycythemia receiving no therapy.

The second case, a woman of 56, was found to have polycythemia four years ago. She was treated with acetylphenylhydrazin under the direction of Dr. Helmuth Ulrich.* In July 1937, however, she had a large gastrointestinal hemorrhage and this was repeated in 1939. Since December 1937 she has had no treatment of polycythemia. (Figure 7.)

The third case, a man 58 years old, entered the Robert Dawson Evans Memorial in June 1938. He had cerebral thrombosis as a complication of polycythemia vera when he first was seen. The hemoglobin concentration was around 160 per cent, and the red count over seven million. It was decided to treat this patient by the method of bleeding alone. Repeated bleedings of 1000 c.c. each were made at frequent intervals until the blood-iron level was reduced to a figure within normal limits. In order to accomplish this purpose, five liters of blood were withdrawn within a period of

* We wish to thank Dr. Ulrich for allowing us to report the case and to use these data.

five weeks. The patient very quickly grew to feel much better and reports that he has been in good health since his discharge from the hospital in July 1938. The immediate effect of such treatment on the blood-iron level was striking. (Figure 8.)

In the first case radiation appeared to succeed not only in destroying red cells but also in depleting iron storage. Since then, apparently, it has been impossible for the clinical manifestations of polycythemia to redevelop. It would seem improbable that the present low blood-iron level could be due to a continued effect of radiation lasting for more than two years since the last treatment.

The second case shows that phenylhydrazin had a notable effect in destroying red cells without, however, depleting iron storage. So it was that as soon as the drug was no longer administered the clinical manifestations of polycythemia reappeared. When the amount of stored iron was depleted by roentgen-ray and hemorrhage, however, the polycythemia seemed more permanently controlled.

In the third case five liters of blood, each containing approximately 700 mg. iron, were withdrawn deliberately. Thus the amount of iron in the body was depleted by about 3.5 gm. Should any of these patients again develop an abnormally high blood-iron level, how will they do it? If polycythemia vera is due primarily to disturbed iron metabolism, conceivably iron in a form not ordinarily used may be drawn upon and thus the blood-iron level may again become excessively high. On the other hand, if polycythemia vera is a true erythremia, there may develop an excessively high red count with a normal blood-iron level, the red cells produced being unable to get enough iron from iron storage to make their iron content normal. That a process of this nature may at times take place in polycythemia vera is suggested by a case which Dr. Marshall N. Fulton of Boston has had under observation for some time and has described to us. This patient, too, had been treated by repeated bleedings. His hemoglobin concentration has been kept within normal limits but his red count remains elevated: thus he has a persistent hypochromia, with excessive numbers of red cells.

There were two cases of polycythemia secondary to congenital heart disease. Clinically, both patients had the tetralogy of Fallot. One of these patients, a young woman 19 years old, had uncomfortable attacks of profound cyanosis. These were so frequent and disturbing that we decided to discover whether ablation of the polycythemia would make any difference to her subjective symptoms. Accordingly blood was withdrawn until the blood-iron level was brought to a point slightly below 47 mg. per cent.

Obviously a large quantity of iron was removed in 2000 c.c. of blood. We were able to reduce the blood-iron level to whatever point was selected. Withdrawal of the blood, however, had no particular effect on the patient's feelings nor did it have any demonstrable effect on the mechanics of her circulation.

Her blood behaved in an interesting fashion. Apparently the stimulation

of chronic cyanosis and anoxemia activated her bone marrow so that the red count rose from a low point of 5.7 million to 8.8 million. There being no iron available, however, she developed a profound hypochromic anemia despite the abnormally elevated red count. Finally she was given iron and as a result the blood-iron level increased, the red count fell, she re-developed a polycythemic hematocrit reading and was brought back to much the same stage she was in before bleeding was undertaken. (Figure 9.)

The second case, another young woman, was under observation in 1936 and again in 1939. Between these two periods there had been no therapy. The blood-iron level behaved most remarkably during this interim. (Figure 10.)

Apparently this patient's blood-iron plethora has largely disappeared. No appreciable change in the heart condition has taken place and the mechanics of the circulation are unchanged. There is no history of blood loss. Is it possible that the high blood-iron level has disappeared and readjustments have been made because there no longer is iron enough available in storage to maintain so high a level?

The iron plethora of polycythemia may now be treated with success in various ways. But the fact of the matter is that very little is known of the essential nature of the condition.

The remainder of the cases with an abnormally high level of blood-iron were an odd lot difficult to classify satisfactorily. A certain number were patients who were moderately dehydrated at entry to the hospital and after rest in bed with adequate fluid intake their blood-iron values promptly fell to normal. Others, particularly a group of middle-aged rather stout men with moderate hypertension seemed to be full-blooded individuals without showing any particular reason for thinking that their full-bloodedness was of clinical significance. A few, strangely enough, were anemic patients, particularly with pernicious anemia, who under treatment seemed to over-correct and developed for varying lengths of time iron plethora. A certain number of cardiacs in decompensation had abnormally high blood-iron levels which became normal as cardiac compensation was regained. Thus there seem to be several factors which may lead temporarily to an abnormally high blood-iron level. Out of the hodge-podge of our material, however, the cases of polycythemia vera and of marked secondary polycythemia were the striking ones. The other cases were too indefinite to be worth more than very brief mention.

In summary, we believe that a knowledge of the blood-iron level is of clinical usefulness. The blood-iron level indicates by an accurate chemical method the hemoglobin concentration of the circulating blood and also gives indirect evidence concerning the amount of iron stored within the body.* The factors of storge of iron and transport of iron are each of importance in the accurate diagnosis and treatment of patients with anemia or polycythemia.

* Direct evidence as to the amount of iron available for hemoglobin production is given by the measurement of serum iron, the level of which must necessarily be interpreted in terms of the total blood-iron. The significance of serum iron estimations has already been discussed by one of us,[4] and this portion of the study of iron metabolism has been purposely omitted from this paper for considerations of unity and brevity.

A knowledge of the blood-iron level is proving, in our experience, of considerable practical interest.

BIBLIOGRAPHY

1. Wong, S. Y.: Colorimetric determination of iron and hemoglobin in blood, Jr. Biol. Chem., 1928, lxxvii, 409–412.
2. Evelyn, K. A.: A stabilized photoelectric colorimeter with light filters, Jr. Biol. Chem., 1936, cxv, 63–75.
3. Sachs, A., Levine, V. E., and Fabian, A. A.: Copper and iron in human blood, Arch. Int. Med., 1935, lv, 227–253.
4. Walker, B. S.: The iron of human blood serum, Jr. Lab. and Clin. Med., 1938, xxiv, 308–315.
5. Moore, C. V., Doan, C. A., and Arrowsmith, W. R.: The mechanism of iron transportation: its significance in iron utilization in anemic states of varied etiology, Jr. Clin. Invest., 1937, xvi, 627–648.
6. Barkan, G., and Schales, O.: Chemischer Aufbau und physiologische Bedeutung des "leicht abspaltbaren" Bluteisens, Ztschr. f. physiol. Chem., 1937, ccxlviii, 96–116.
7. Barkan, G.: Über das leicht abspaltbare Bluteisen und sein Verhältnis zum Hämoglobin, Ibid., 1927, clxxi, 179–193.
8. Klumpp, T. G.: The variability of non-hemoglobin iron, Jr. Clin. Invest., 1935, xiv, 351–355.
9. Barkan, G.: Die optische Bestimmung des Blutfarbstoffs als Oxyhämoglobin, Hämoglobin und Hämatin und die Zuverlässigkeit der Ergebnisse, Biochem. Ztschr., 1937, ccxciv, 239–248.
10. Hoskins, R. G., and Sleeper, F. H.: The effects of ingested thyroid substance on the blood morphology of man, Endokrinologie, 1929, v, 89–103.

SPLEEN SIZE IN PERNICIOUS ANEMIA *

By Edward Bigg, M.D., *Chicago, Illinois*

A palpable spleen has long been accepted as an expected finding in the physical examination of a patient suffering from pernicious anemia. Although Sturgis [11] reported the spleen to be rarely palpable and Minot [7] pointed out that it was palpable in only 5 per cent of his cases, the majority of standard textbooks and monographs on pernicious anemia give the incidence as from 20 to 50 per cent.

Evans [3] reported the spleen to be palpable in 20 per cent of his cases. In McCarty's [6] series of 51 cases the spleen was palpably enlarged in 45 per cent. Cornell [2] stated that the "spleen is not infrequently enlarged," and points out that this enlargement is important in the differential diagnosis, as it may confuse the disease with endocarditis, leukemia, polycythemia, and Gaucher's disease. Stevens [10] noted that slight or moderate enlargement of the spleen is frequently observed, and that occasionally the organ may extend almost to the level of the umbilicus. Wintrobe and Musser [13] reported that the spleen is moderately increased in size in 40 per cent of cases and palpable in 25 per cent. Ordway and Gorham [9] found that in one-third to one-half of their cases it is palpable and occasionally markedly enlarged. Kracke and Garver [4] mentioned that the spleen may be enlarged sufficiently so that it may be palpated in less than one-half of the cases. Meakins [8] reported that in 30 per cent of the cases the spleen is definitely palpable. Suarez [12] used the presence of a palpable spleen as a diagnostic aid in differentiating pernicious anemia from tropical sprue.

Materials and Methods

The material used for this report is based on the records of patients seen and treated at the Simpson Memorial Institute for Medical Research. Two hundred consecutive case records were reviewed. Each of these patients has been examined by at least six different physicians, each of whom recorded his findings independently. The diagnosis of pernicious anemia was established by complete histories, physical examinations, and laboratory studies. All cases showed the expected response to specific anti-pernicious anemia therapy. A total of 18 autopsies was done; only one of the patients with a palpable spleen had a postmortem examination.

Data

One hundred and ten cases examined were males, and 90 were females. The ages varied from 21 to 80. The duration of the symptoms ranged

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From the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan.

from two months to 10 years. One hundred and twenty-four patients had no previous treatment, 19 were in remission, and 57 were in relapse. The red blood cell counts varied from 500,000 to 5,000,000 per cubic millimeter.

Of the 200 cases reviewed, there were six (3 per cent) in whom the spleen was palpable. More complete and specific data concerning these six cases are contained in the table. The red blood cell measurements of these individuals differed from those of the others in the series in that the diameters of the majority of the cells were less than 7.5 microns. Examining the stained cells, it was noted that the largest percentage of them were small in diameter, but were spherical in appearance. In one case (B. V.) in which the cells were tested, their resistance to hypotonic salt solution was less than normal.

In a total of 18 autopsies the weight of the spleen varied from 95 grams to 640 grams, the average being 265 grams. In 17 of the autopsies performed the spleen was larger than the normal weight of 150 grams, although but one was palpable. This value for "normal" was obtained from Krumbhaar and Lippincott's [5] recent study of a series of 4,000 postmortem examinations in traumatic deaths and diseases not associated with splenomegaly. An autopsy was carried out in only one individual in whom the spleen was palpable. A summary of this case follows:

Case Report

The patient was a 54 year old white male who was admitted complaining of weakness, tiring easily, pallor, dyspnea, and palpitation of the heart on mild exertion. These symptoms had been present for six months. His appetite had been poor, and there had been a weight loss of 50 pounds. Soreness of the tongue had never been noticed. There were no paresthesias.

Physical examination: The essential features were pallor of the skin and mucous membranes, gray hair, blue irides, dyspnea at rest. The heart was moderately enlarged, with loud hemic murmurs at the apex and base. Blood pressure was 150 systolic and 80 diastolic. Transitory coarse râles were heard at both lung bases. The tongue showed early atrophy of the papillae. The liver edge was palpable just below the right costal margin. The spleen was palpable five centimeters below the left costal margin; it was firm and not tender. There was moderate pitting edema of the lower extremities. Neurological examination was negative.

Examination of the blood: Red blood cells 760,000 per cu. mm.; hemoglobin 18 per cent (S); white blood cells 6,350 per cu. mm.; polymorphonuclear neutrophiles 68 per cent; lymphocytes 27 per cent; monocytes 3 per cent; eosinophiles 1 per cent. There were many immature red blood cells with nucleated forms and occasional poikilocytes. Red blood cell measurements: 45 per cent of the red blood cells were smaller than 7.5 microns; 33 per cent were 7.5 microns; and 22 per cent were larger than 7.5 microns. Gastric analysis was not done because of the poor condition of the patient.

The patient was digitalized immediately, given transfusions and intravenous liver extract. There was a reticulocyte response to 34.5 per cent on the seventh day of treatment. He ran a progressively downhill course, however, and died on his eighth hospital day. The significant autopsy findings were congestive heart failure, hyperplasia of the bone marrow, and well advanced atrophic cirrhosis. The spleen weighed 640 grams.

Discussion

Unfortunately there were no data on the cell volume of these patients. However, of another group of patients, one with a large spleen showed small red blood cells as in these cases, but the mean corpuscular volume was larger. From this it is surmised that the red blood cell volume in the six cases herein described was also larger, as the cells had the appearance of spherical cells in the stained preparations. In five of the cases complications such as cholecystitis, cholelithiasis, cirrhosis of the liver or congestive heart failure were contributing causes of splenomegaly. In one case no evident accessory cause for a palpable spleen was apparent.

During the past decade great advances have been made in our concept of anemias. There can be little doubt that many cases of macrocytic anemia which were formerly classified as pernicious anemia are today recognized as different entities. The macrocytic anemias associated with pregnancy, food deficiency, fish tapeworm, myxedema, carcinoma of the stomach and cirrhosis of the liver are examples of such previous erroneous diagnoses. The case reported above illustrates the difficulty in differentiating the last named condition from pernicious anemia. Although it cannot be said that the five other cases with enlarged spleen also had cirrhosis of the liver, it is of interest to note that the stained blood preparations deviated from the classical expected finding.

It appears that the incidence of a palpable spleen is definitely less than has heretofore been believed. It further appears that this decrease is more likely dependent upon more exact methods of diagnosis and more thorough understanding of the disease, rather than upon the institution of specific therapy as suggested by Minot.[7] The presence of a palpable spleen is of such rarity that if it occurs in a patient suspected of having pernicious anemia it suggests the possibility either of a complication or of another disease.

Most of the spleens examined at autopsy were larger than normal. It is evident that a spleen may be increased 400 per cent in weight without being palpable. In Askanazy's [1] summary of spleen weights in 461 cases of pernicious anemia, reported from different parts of the world, 321 (69.6 per cent) had spleens weighing over 150 grams. The largest weighed 1200 grams. Causes for splenomegaly in this series were given as active and passive hyperemia, hyperplasia, hematopoiesis, and occasionally infection.

Conclusions

1. In a series of 200 consecutive cases of pernicious anemia the spleen could be palpated in 3 per cent.
2. The red blood cells in these six individuals were presumably spherical
3. One patient was proved at autopsy to have cirrhosis of the liver.
4. In 18 cases which came to autopsy, there was some degree of enlargement of the spleen in 94.6 per cent. In only one of these cases was the spleen palpable.

5. The presence of a palpable spleen in a patient suspected of having pernicious anemia is of such rarity that it suggests the possibility either of some complication or of some other disease.

TABLE I

Data on the 6 Cases in This Series in Which the Spleen Was Palpable

Patient	Sex	Age	Status	Duration of Symptoms	R.B.C. Millions per cu. mm.	Lower Edge of Spleen	Complications
M. B.	F	46	Untreated	1½ yrs.	0.97	5 cm. below L.C.M.	Cholecystitis with cholelithiasis
A. B.	F	51	Relapse	2 yrs.	0.5	3 cm. below L.C.M.	Spleen no longer palpable after institution of treatment
A. T.	M	54	Untreated	6 mos.	0.79	5 cm. below L.C.M.	Congestive heart failure; cirrhosis of liver
B. V.	F	57	Relapse	5 yrs.	1.1	4 cm. below L.C.M.	Marked congestive heart failure; hypertensive heart disease
E. P.	M	40	Relapse	1½ yrs.	1.4	7 cm. below L.C.M.	Congestive heart failure
M. F.	F	33	Untreated	2 yrs.	1.8	3 cm. below L.C.M.	None

BIBLIOGRAPHY

1. ASKANAZY, M.: Die pathologische Anatomie der Anaemien, Compt. rend. d. b. Troisième Conférence Internationale de Pathologie Géographique, 1937, Helsingfors, p. 32.
2. CORNELL, B. S.: Pernicious anemia, 1927, Duke University Press, Durham, p. 115.
3. EVANS, F. A.: Pernicious anemia, 1926, Williams and Wilkins Company, Baltimore, pp. 79 and 109.
4. KRACKE, R. K., and GARVER, H. E.: Diseases of the blood and atlas of hematology, 1937, J. B. Lippincott, Philadelphia, p. 230.
5. KRUMBHAAR, E. B., and LIPPINCOTT, S. W.: Postmortem weight of "normal" human spleen at different ages, Am. Jr. Med. Sci., 1939, cxcvii, 344.
6. MCCARTY, W. C.: Chronic splenomegaly, Arch. Int. Med., 1928, xli, 536.
7. MINOT, G. H., *in* MUSSER, J. H.: Internal medicine, 1938, Lea and Febiger, Philadelphia, p. 948.
8. MEAKINS, J. C.: The practice of medicine, 1938, C. V. Mosby, St. Louis, p. 523.
9. ORDWAY, T., and GORHAM, L. W.: Diseases of the blood, Oxford monographs on diagnosis and treatment, Vol. 9, 1937, Oxford University Press, New York.
10. STEVENS, A. A.: The practice of medicine, 1931, W. B. Saunders, Philadelphia.
11. STURGIS, C. C., *in* MUSSER, J. H.: Internal medicine, 1938, Lea and Febiger, Philadelphia, p. 948.
12. SUAREZ, R. M.: Clinical and hematologic review of sprue, Puerto Rico Jr. Pub. Health and Trop. Med., 1938, xiv, 157.
13. WINTROBE, M., and MUSSER, J. H.: Diseases of the blood, *in* TICE, FREDRICK: Practice of medicine, Vol. 5, p. 841.

CAPILLARY RESISTANCE IN ARTIFICIALLY INDUCED FEVER *

By PHILLIP L. ROSSMAN, M.D., *Cleveland, Ohio*

IN an attempt to explain the mechanism of hemorrhage in artificially induced fever, studies of capillary resistance by means of the suction test were made on 12 subjects, three of whom were used twice, making a total of 15 observations.

The outstanding pathologic observations in experimental animals and human subjects following induced fever have been the presence at autopsy of focal hemorrhages and acute parenchymatous degeneration of the organs. Giles, Harvey and Dampere,[1] in a study of the effect of exogenous heat on rabbits, saw marked focal hemorrhages in the viscera and central nervous system on examination of the non-surviving animals. Hyperemia and cloudy swelling of the organs, as well as degenerating lesions in the male generative epithelium, were noted. In a study of two human beings and 20 experimental animals under accurately controlled fever conditions, Hartman and Major [2] described pathologic changes consisting of engorgement of blood vessels, especially of capillaries, hemorrhage and degeneration of the adrenal cortex, hemorrhages in the brain, edema and congestion of the lungs, and parenchymatous degeneration of the liver and kidneys. Schnabel and Fetter,[3] Watts and Hartman,[4] and Wilbur and Stevens [5] report similar observations.

METHOD

The suction test consists in the application of a small cup with an inside diameter of 1 cm. to the volar surface of the forearm just below the antecubital fossa. A negative pressure is then maintained for one minute at a given level as determined by a mercury or aneroid manometer (figure 1). The capillary resistance is considered to be the lowest negative pressure required to produce at least two macroscopic petechiae. This test is probably the simplest and most accurate method of measuring frequent fluctuations in capillary resistance. It was first described by Hecht [6] in 1907, and has been used widely in the study of scurvy and hemorrhagic diseases.

Dalldorf [7] and others have pointed out inherent weaknesses in the suction test. There are many variables such as thickness, texture and color of the skin even in the same individual. Spontaneous hemorrhages may occur, necessitating examination of the skin before the suction cup is applied. Petechiae are difficult to see in negroes due to the skin pigmentation. The tourniquet test, flicking test, and intradermal venom test are also used to study capillary resistance, but they have further disadvantages in that they

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do not lend themselves to quantitative determinations and are not adaptable to measure rapid fluctuations which may occur.

In this study artificial fever was induced by means of the Kettering hypertherm, a sealed air conditioned box in which the patient's body, except the head, lies entirely free on a rubber air mattress. Stecher and Solomon [8]

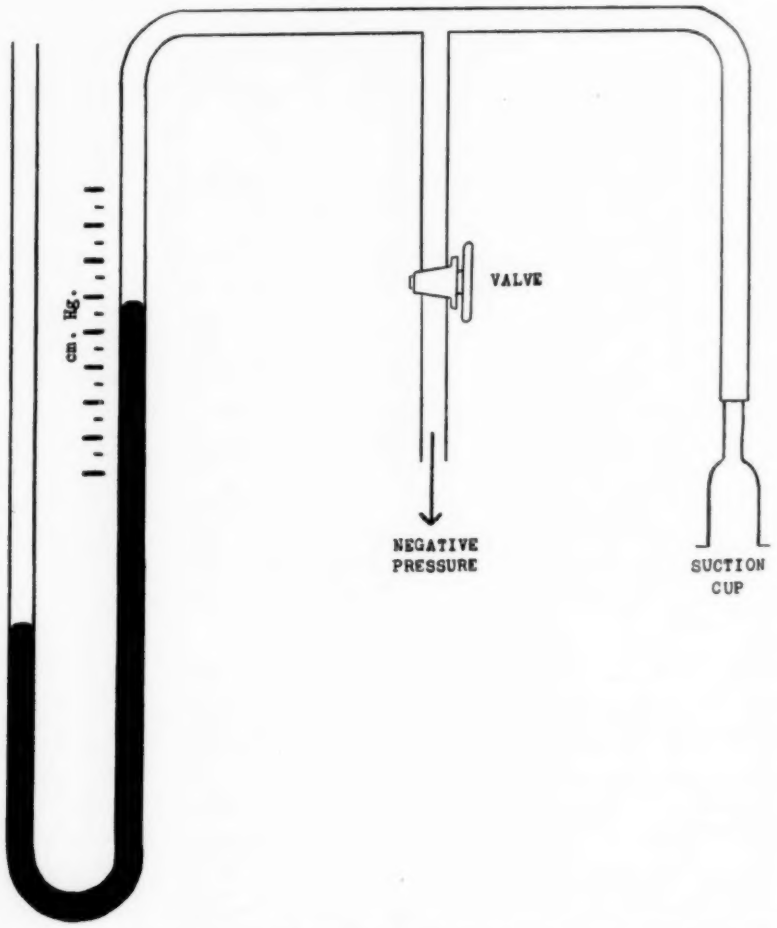

FIG. 1. Schematic diagram of apparatus used to determine capillary resistance.

give a more detailed description of the procedure followed. The suction cup was applied to the patient's forearm through a partially opened panel door of the fever chamber. Opening this door usually caused the temperature of the cabinet to fall from two to five degrees (F.), but the loss was quickly restored when the door was closed.

Observations were made on 12 patients, seven males and five females, whose ages ranged from 8 to 53 years. They had the following diseases: atrophic arthritis, gonorrheal arthritis, gonorrheal urethritis, ankylosing

spondylitis, general paresis, rheumatic heart disease, chorea, and chronic ulcerative colitis. The patients were in the cabinets from three to six and a half hours. No attempt was made to correlate such related factors as skin temperature, blood pressure, platelet and blood counts, prothrombin and fibrinogen determinations, bleeding and clotting times, blood oxygen and carbon dioxide determinations, etc. Rectal temperatures were recorded by means of a mercury thermometer at each reading of capillary resistance.

Results

Control readings taken before the patients were placed in the fever cabinets varied from 20 to 40 cm. of mercury negative pressure. These were within the normal range obtained by Dalldorf [7] and others. At time intervals varying from two to 20 minutes after the patient was placed in the fever cabinet there occurred in all instances an increase in the ease of producing capillary hemorrhage. Negative pressure readings fell from 5 to 30 cm. of mercury. To obtain the rate of fall, readings were taken every few minutes after the patient was placed in the hypertherm. The exact rate of change could not be determined in most instances, because time was frequently lost in making the trial determinations necessary to get the lowest negative pressure which would produce at least two petechiae. The initial drop was usually greatest when the control reading was high. The lowest resistance obtained was 7.5 cm. of mercury. In 11 out of 15 observations readings were reduced to either 10 or 15 cm., definitely abnormally low results as compared to normal standards.

In seven instances capillary resistance remained at a constant low level during the entire treatment. The other eight showed a fluctuation of 5 to 10 cm. In the former group there may have been fluctuations which occurred during a non-observation period. Spontaneous hemorrhages of the skin were not observed at any time. The patients perspired freely during the treatments.

A rapid decrease in the ease of producing petechiae occurred when the patients were removed from the hypertherm. This was noted regardless of the duration of the treatment. Readings rose to a minimum of 25 and a maximum of 65 cm. of mercury usually within a period of a few minutes. In 13 of the 15 records the post-treatment increase in capillary resistance exceeded the initial control reading by 5 to 40 cm. of mercury. The remaining two records showed a return to the same level as the control.

At intervals of two to eight hours after the treatments seven readings were above, three were below and five were the same as the control readings. Most of the experiments were terminated after a total of eight hours. Figure 2 shows four records of capillary resistance obtained during fever treatments.

There was no quantitative correlation of body temperature (rectal) and capillary resistance. A given body temperature during the onset of fever did not produce the same capillary resistance as did that same temperature

during the recession of fever. Figure 3 shows representative temperature and capillary resistance curves during a typical fever treatment.

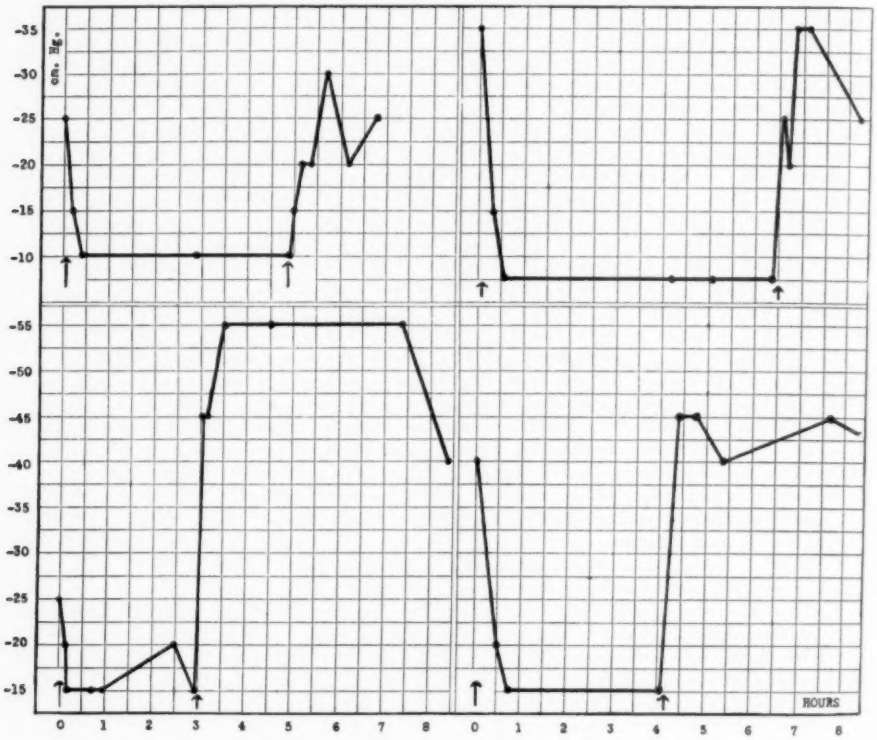

FIG. 2. Capillary resistance in four patients during artificially induced fever. The arrows denote the beginning and end of the treatments.

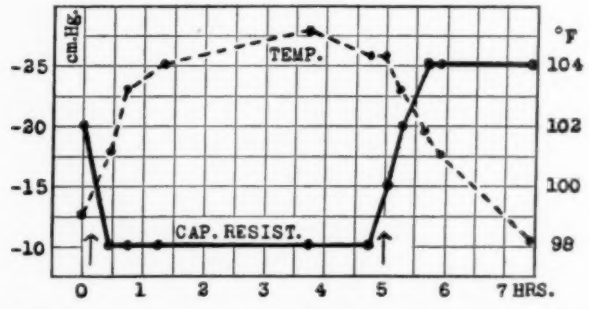

FIG. 3. Rectal temperature and capillary resistance during an artificially induced fever treatment. The arrows denote the beginning and end of the treatment.

Observations on three patients were repeated at a later date. The second curves were similar but not exactly comparable to the initial ones.

Other studies on the localized application of heat to one arm by means of a heat lamp or by inserting one arm in a fever cabinet also showed a re-

duction in capillary resistance and a period of hyperresistance after the heat was removed. The opposite arm, used as a control, showed no change. Two patients with neurosyphilis who were inoculated with tertian malaria, and two others who were given fever treatments by means of typhoid-paratyphoid vaccine, showed similar changes in capillary resistance during the febrile period, but to a lesser degree.

To study the histologic structure of petechiae produced by means of a suction cup, eight biopsies were taken on four patients not included in the present study. The microscopic picture in general showed pools of extravasated blood between the bundles of collagen in the subpapillary layer (corium) of the skin. The red cells showed a tendency to grouping about small arterioles and sweat glands. Serial sections were not made, but one section showed an interruption in the wall of an arteriole, with blood extending from the lumen into the surrounding tissue. There was no associated inflammatory reaction. Similar biopsies done by Peck, Rosenthal, and Erf [9] showed dilated, moderately engorged capillaries in the papillary and subpapillary layers of the skin. Some of the vessel walls were ruptured. Spaces between endothelial cells in intact capillaries were widened. No inflammatory exudate was seen. There was fragmentation of elastic tissue in the area of hemorrhage.

Discussion

Wolbach and Howe [10] explained the decreased capillary resistance and hemorrhages seen in experimental and clinical scurvy on the basis of a chemical alteration of intercellular substances. Johnson, Osborne, and Scupham [11] determined finger-volume changes during fever therapy by means of an air conduction plethysmograph. They obtained an increase in pulse-volume which was interpreted as increased circulation due to vasodilatation. Landis [12] concluded from his microinjection studies that "heat produces peripheral vasodilatation, raises capillary blood pressure conspicuously and, through relaxation of capillaries, increases the area of capillary wall available for filtration." Dilated capillaries are probably more easily ruptured than those of normal caliber. Also, with greater intracapillary pressure [13] it would seem that less extracapillary suction would be necessary to rupture the vessel walls. Hartman [14] showed that the pathologic changes resulting from fever therapy were typical of anoxia produced by prolonged asphyxia.

Wilson and Doan,[15] in a study of blood coagulating factors, concluded that the anoxia produced by artificially induced fever resulted in hepatic and megakaryocytic damage. This in turn caused a decrease in prothrombin alone or with fibrinogen, and a relative or absolute thrombocytopenia. In two of their patients epistaxis and hematemesis occurred at the point of greatest depression in circulating prothrombin and blood platelets. According to the theories on blood clotting, these factors are concerned not with hemorrhage, but rather with the clotting mechanism after hemorrhage occurs. Yet recent investigations have shown that the hemorrhagic tendency asso-

ciated with obstructive jaundice was due to a low plasma prothrombin. The prothrombin level was restored and bleeding successfully controlled by the use of vitamin K and bile salts.[16] The use of these substances as a prophylactic measure may be indicated in therapeutic hyperthermia in view of the low plasma prothrombin which occurs.

The lowered capillary resistance only at the site of application of heat demonstrates that the phenomenon does not depend on systemic changes and can be purely a local reaction.

Changes in peripheral and visceral capillary resistance during artificially induced fever are probably not concomitant. According to Bazett,[17] exposure of the body to heat causes an increase in the blood volume of the skin due to the dilatation of arterioles, capillaries and veins. At the same time there is a compensatory constriction in the central vessels, particularly in the splanchnic area, so that, with the more or less maintained peripheral resistance and volume of the vascular bed, there is only slight diminution, if any, in cardiac output and blood pressure. An increase in blood volume is the alternative adjustment mechanism to compensatory vasoconstriction. Bazett [17] showed that this may occur with exposure to heat prolonged for a period of days, but no valid evidence has been advanced of acute increases in blood volume exceeding 10 per cent of the normal value for short exposures.

If the tendency to hemorrhage in visceral organs is dependent at all upon capillary resistance, then this tendency is probably greatest when the patient is removed from the fever cabinet at the end of the treatment. At this time the skin capillaries become highly resistant, presumably due to a central shift in blood distribution as a result of peripheral vasoconstriction and visceral vasodilatation. Further investigation may show that it is best to reduce cabinet heat slowly at the end of a treatment instead of suddenly taking the patient out of the fever cabinet and causing a rush of blood from the periphery to the visceral organs.

Summary

1. Artificial fever, induced by means of the Kettering hypertherm, produced an immediate decrease in capillary resistance as determined by the suction test applied to the skin of the forearm.

2. A quick return of the skin capillaries to normal resistance, with a temporary hyperresistance in many instances, occurred following a fever treatment.

3. The focal hemorrhages seen at autopsy following artificially induced fever in experimental and clinical subjects may be due to decreased capillary resistance.

4. The exact cause of this decreased capillary resistance is as yet unknown. Vasodilatation and increased intracapillary pressure are probably the underlying factors.

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REFERENCES

1. Giles, U., Harvey, A. L., and Dampere, F. W.: Sterility of male animals induced by radiant heat, Arch. Phys. Therap., 1938, xix, 619.
2. Hartman, F. W., and Major, R. C.: Pathological changes resulting from accurately controlled artificial fever, Am. Jr. Clin. Path., 1935, v, 392–410.
3. Schnabel, T. G., and Fetter, F.: Fever therapy in gonorrheal arthritis and chorea, Ann. Int. Med., 1935, ix, 398.
4. Watts, F., and Hartman, F. W.: Abstracts of papers and discussions. Fifth Annual Fever Conference, Dayton, Ohio, May 1935.
5. Wilbur, E. L., and Stevens, J. B.: Morbid anatomic changes following artificial fever, with report of autopsies, South. Med. Jr., 1937, xxx, 286.
6. Hecht, A. F.: Experimentell-klinische Untersuchungen über Hautblutungen im Kindesalter, Jahrb. f. Kinderh., 1907, lxv, 113. Erg. Heft.
7. Dalldorf, G.: A sensitive test for sub-clinical scurvy in man, Am. Jr. Dis. Child., 1933, xlvi, 794.
8. Stecher, R. M., and Solomon, W. M.: The complications and hazards of fever therapy: analysis of 1000 consecutive fever treatments with the Kettering hypertherm, Ann. Int. Med., 1937, x, 1014.
9. Peck, S. M., Rosenthal, N., and Erf, L. A.: Purpura: classification and treatment, with special reference to treatment with snake venom, Arch. Dermat. and Syph., 1937, xxxv, 831.
10. Wolbach, S. B., and Howe, P. R.: Intercellular substances in experimental scorbutus, Arch. Path. and Lab. Med., 1926, i, 1.
11. Johnson, C. A., Osborne, S., and Scupham, G. W.: The effect of artificial fever on the pulse volume changes of the finger, Am. Jr. Med. Sci., 1935, cxc, 485.
12. Landis, E. M.: The passage of fluid through the capillary wall, Am. Jr. Med. Sci., 1937, cxciii, 297.
13. Landis, E. M.: Micro-injection studies of capillary blood pressure in human skin, Heart, 1930, xv, 209.
14. Hartman, F. W.: Lesions of brain following fever therapy: etiology and pathogenesis, Jr. Am. Med. Assoc., 1937, cix, 2116.
15. Wilson, S. J., and Doan, C. A.: Pathogenesis of hemorrhage in artificially induced fever, Ann. Int. Med., 1940, xiii, 1214.
16. Butt, H. R., Snell, A. M., and Osterberg, A. E.: The use of vitamin K and bile in treatment of the hemorrhagic diathesis in cases of jaundice, Proc. Staff Meet. Mayo Clin., 1938, xiii, 74.
17. Bazett, H. C.: The effect of heat on the blood volume and circulation, Jr. Am. Med. Assoc., 1938, cxi, 1841.

THE TREATMENT OF HYPERTENSION; MEDICAL VERSUS SURGICAL *

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The title of our presentation was not intended to imply a conflict between the medical and the surgical treatment of hypertension. Rather, it was worded to express an attempt to evaluate the respective merits of these two methods of treatment. As internist and neurosurgeon, our primary interest in hypertension and that of our clinical associates is a therapeutic one; we want to find out what can be done to relieve hypertension and the symptoms which it produces. This report is of a continuation of studies reported earlier.[1-7]

The importance of hypertension as a problem of health needs emphasis. High blood pressure is both a common disease and a serious one. Indeed, it appears to be more common and more deadly than cancer. At The Mayo Clinic, each year, we encounter from five to six thousand patients who have definite hypertension. Cardiovascular-renal disease kills 500,000 people annually in the United States; that is, it kills four times as many people as cancer does. Apparently, hypertension accounts for from a half to three-fourths of all deaths referable to cardiovascular-renal disease, and thus is from two to three times as deadly as cancer.[8, 9] † About a fourth of all deaths of individuals past 50 years of life is referable to hypertension.[10] Keith, Wagener and Barker have shown that the mortality in hypertension,[11] groups 1 and 2, is 30 and 42 per cent, respectively, in four years from the time of their diagnosis; whereas, for a similar period, the mortality of hypertension, group 3, is 78 per cent and in group 4, it is 98 per cent.[11] Among subjects who have systolic blood pressures of about 170 mm. of mercury, the relation of actual mortality to expected mortality according to insurance statistics is as 219.6 to 100; among those patients whose systolic blood pressures exceed 200 mm. of mercury the actual mortality is to the expected as 827.5 is to 100.[10, 12] For individuals more than 40 years of age, systolic blood pressure ranging from 35 to 44 mm. in excess of normal increases the expected mortality two and a half times. Such a slight increase in blood pressure as that represented by the figures 170 to 174, systolic, and 106, diastolic, expressed in millimeters of mercury, increases the expected mortality two and a half times.[13]

Many physicians appear to be misled by the observation that an occasional patient survives hypertension for many years. They may then believe that

* Read before the meeting of the American College of Physicians, Cleveland, Ohio, April 2, 1940.

† On this basis, the estimated mortality from hypertension would be 250,000 to 375,000 deaths annually in the United States. Another author estimated in 1924 that 140,000 deaths were caused annually by hypertension.

hypertension in general is not very serious. Such an attitude is wishful in part, for few physicians like to face the fact that there is no routinely effective treatment for hypertension. If the physician believes that hypertension is not a serious disease, failure to treat it satisfactorily will not be so disappointing. This belief in the benignity of hypertension neglects to take into account repeated observations such as those written in the preceding paragraph; namely, that hypertension usually is a serious disease which terminates the lives of those it afflicts within a relatively short span. Another cause for concern is the apparently decreasing age at which hypertension endangers the lives of those who are afflicted with it. This is a clinical impression based on the repeated observations that hypertensive members of a third generation die earlier than hypertensive members of the second generation of the same family, and that those of the second generation die earlier than those of the first generation; apparently all from hypertension. Not uncommonly on questioning, the physician finds a situation similar to the following: the grandfather died at 72 years of age of "stroke"; the mother died at 60 of "Bright's disease" and the son, aged 35 years, is seriously ill from hypertension which probably will terminate his life within a few months. All these observations emphasize the fact that hypertension is ordinarily a serious disease.

During the past few years there has been much progress in the production of hypertension experimentally and in understanding of the mechanism by means of which the blood pressure is elevated in such experiments. A prominent example is the notable achievement of Goldblatt,[14] who produced elevation of the blood pressure in animals by diminishing the blood supply to the kidneys. For these experiments, in which he produced a condition in animals closely resembling essential hypertension of man, Goldblatt received the Phillips Memorial Prize at the meeting of the American College of Physicians two years ago. It is unnecessary to refer specifically herein to others who have confirmed and extended Goldblatt's observations. The names of Page, Winternitz, Collins, Dock, Freeman, Houssay, Introzzi, Katz, Leiter, Nuzum, Prinzmetal, Rytand, Wilson, Landis, Pickering and Wood, are prominent in this field.* We do not wish to detract from the excellent work that has been done on experimental hypertension and allied studies; rather, we wish to commend such work as being praiseworthy evidence that advances are occurring in a field of medicine in which little progress has been made until recently. We feel, moreover, that we will not detract from this excellent experimental work if we indicate that it has helped only slightly the clinician who must attend patients who have hypertension. We hope, also, that this statement will not be true for long. These few introductory remarks serve to emphasize the fact that hypertension is a common and serious disease, and that recent experimental studies have helped only insignificantly in the successful treatment of it up to the present time.

* These contributions are reviewed in Hipertensión Arterial Nefrógena; Estudio Experimental. Ferrari Hnos. Buenos Aires, 1939.

Medical Treatment

Since hypertension is produced by increased resistance offered to the flow of blood through the arterioles, the specific need in medical treatment is a preparation which will restore arteriolar resistance to normal and which will not produce harmful or unpleasant side effects. Unfortunately, such a preparation is not available now.

It is well to state herein that the belief which persists stubbornly that it is inadvisable to lower blood pressure in the presence of essential hypertension has no foundation in fact. Vital functions continue normally when blood pressure is reduced and we doubt that reduction of blood pressure in itself is ever harmful. We believe that such a reduction is highly desirable in hypertension. Many drugs have been recommended for the treatment of hypertension. The very number of them convicts them of comparative or actual uselessness. There is surprisingly little evidence in the medical literature to indicate that many of the remedies so enthusiastically advertised have virtues. Over a period of years we have tried many of them without being convinced that they have any specific effect on blood pressure.

It has been shown repeatedly that blood pressure is not static but is labile. This is particularly true in the presence of hypertension, when the blood pressure fluctuates greatly.[15, 16] We have shown that if the systolic blood pressures of a group of patients in the clinic were more than 200 mm. of mercury, subsequent readings in the hospital would show that the systolic blood pressure decreased an average of about 50 mm. of mercury and that the average for the diastolic blood pressure decreased about 35 mm. of mercury, when no specific treatment was administered.[17] If all physicians who wrote of reduction of blood pressure as resulting from some specific method of treatment would determine the blood pressure of their patients hourly for 24 consecutive hours, they would not err in attributing to some specific method of treatment those reductions in blood pressure which occur without specific treatment. There can be but little doubt that the popularity of many remedies is based on observation of diminution of blood pressure; a diminution which has occurred spontaneously and has not resulted from a specific remedy.

The nitrites, purine derivatives (for example, theobromine and theophylline), iodides and extracts of tissue are probably of little or no value in the treatment of hypertension.[10] Too frequently a remedy achieves popularity because of its supposed beneficial effects which are found to be absent when careful studies are carried out. Such is the case of bismuth subnitrate.[18, 19] Occasionally, when hypertension develops during the menopause, there may be reduction of it as a result of the administration of ovarian follicular hormone or placental hormone. However, it is inadvisable to continue to treat such patients over long periods with these hormones for the purpose of reducing the blood pressure unless a definite reduction of the blood pressure can be shown to follow adequate dosage

rather promptly. Of all the drugs commonly used in the treatment of hypertension, excepting potassium sulfocyanate, the sedatives are the best and of these phenobarbital is as good as any. The ideal sedative is one which will reduce nervousness and irritability but which will not interfere with the essential cerebral activities. Ordinarily, ½ to 1½ grain (0.032 to 0.1 gm.) of phenobarbital administered three times a day is advisable.

Potassium sulfocyanate has been used in the treatment of hypertension for several years.[20, 21] A relatively recent and important advance has been determination of the concentration of the cyanates in the blood.[8, 22, 23] The amount of this drug to be administered orally should be determined by frequent calculations of the concentration of cyanates in the blood. The concentration in the serum should range between 8 and 14 mg. in each 100 c.c. of blood. As little as a total of 5 grains (0.3 gm.) a week, or as much as 5 grains (0.3 gm.) three times daily, of potassium sulfocyanate, depending of course on the individual patient, must be administered to cause the aforementioned concentration in the blood. Such symptoms as headache, insomnia and nervousness may be relieved thereby. Blood pressure is reduced in about half the patients so treated.[8, 22] Fatigue, weakness, increasing nervousness, dermatitis, nausea, vomiting, anemia and enlargement of the thyroid gland may occur, even if administration of the drug is well controlled. Weakness and fatigue may occur early in the course of adequate treatment, but usually they disappear as medication is continued. After five to ten years of treatment, elderly patients who have severe grades of hypertension may have anemia, emaciation and muscular wasting, but it is not clear whether these conditions result from cyanate therapy or from hypertension itself. If the concentration of cyanates in the blood is too great, lethargy, mental confusion, psychosis, exfoliative dermatitis, weakness, difficulty of speech, convulsions and collapse may occur.[8, 22, 24]

Our experience with the use of sulfocyanate in the treatment of hypertension has been somewhat limited, but relief of symptoms such as headache is frequently striking. There is definite reduction of blood pressure in some cases. Potassium sulfocyanate never should be administered for a long period unless the amount administered is based on studies of concentration of cyanates in the blood of each individual patient. It is imperative that the physician prescribing sulfocyanates familiarize himself with the literature on the subject before treating the patient with the drug. Not only does the administration of potassium sulfocyanate help patients who have not undergone sympathectomy for hypertension, but in some of the cases in which little or no benefit has been obtained from this operation, the postoperative administration of potassium sulfocyanate has been followed by most gratifying results. Davis and Barker [25] have noted similar results.

Rest and the reduction of nervous stresses and strains are advisable in the treatment of many patients who have essential hypertension. In general, it is advisable for patients who have hypertension to obtain nine hours of rest in bed at night, to lie down for an hour or an hour and a half in the

middle of the day, to take vacations frequently, to acquire a calm, philosophic outlook on life and to avoid nervous stresses and strains. Young individuals who follow occupations that are strenuous from a nervous standpoint may well consider it advisable to change to an occupation that is more restful.

Many diets have been advised for the treatment of hypertension, but there is very little evidence that diet influences blood pressure. We do not feel it advisable to restrict protein or salt in diets of hypertensive patients who do not have renal or myocardial failure. Individuals who are overweight should reduce, for obesity throws an additional strain on the heart by increasing the work that the heart must do, and as a result of deposition of fat in cardiac muscles and around the heart. Restriction of alcohol and coffee is not imperative unless they serve as stimulants. They do not in themselves increase the blood pressure appreciably. Smoking greatly increases the blood pressure of many patients who have hypertension, and if this can be demonstrated by having the patient smoke after his blood pressure has reached a basal value, it is well to consider sharp restriction or complete elimination of smoking.

It is apparent that the methods of medical treatment available today are largely unsatisfactory, so far as reduction of blood pressure is concerned. That they have some value is apparent, but we believe that almost every physician who treats hypertension is dissatisfied with such therapeutic methods as are available to him today. Symptoms may be relieved rather easily, as Ayman [26] has pointed out. However, continued relief of symptoms may be considerably more difficult to accomplish than is temporary relief of them. This conclusion relative to failure of reduction of blood pressure by medical means is supported by the opinion of almost all those who treat patients who have high blood pressure under controlled conditions, by the high mortality caused by hypertension and by the number of physicians who consult other physicians or refer their patients to other physicians because the physician's own medical treatment has been inadequate. The situation regarding the medical treatment of hypertension is roughly comparable to that regarding pernicious anemia before the discovery of the efficacy of liver extract. It may surprise younger members of the profession to know that the present-day medical treatment of hypertension is much the same as that outlined 25 years ago by Elliott and that described 20 years ago by Moschcowitz.[27, 28] During the intervening period several million people have died of high blood pressure in the United States. The failure to change this type of medical treatment is patently not referable to the fact that this treatment has been satisfactory but to the fact that there has been nothing better brought forth.

Since the medical treatment of essential hypertension is largely unsatisfactory we have performed sympathectomies with the hope of relieving hypertension. This type of treatment has been employed on the bases of previous experiences with sympathectomies in the treatment of peripheral vascular diseases of vasospastic origin.

Sympathectomy is not carried out because we have assumed that the in-

creased resistance to the flow of blood is localized to the splanchnic region. On the contrary, we accept the evidence that the increased resistance offered to the flow of blood through the arterioles is present over the entire body.[29, 31] If the surgeon is to accomplish the best results from the neurosurgical treatment of hypertension, he should sever the connections of the sympathetic nerves with almost all portions of the body. Unfortunately, this is impracticable or even impossible. We are aware, also, that clinical and experimental evidence is available to indicate that the sympathetic nervous system has little or nothing to do with the elevation of the blood pressure in essential hypertension.[29, 30, 31] Some of this evidence is acceptable and some of it is unacceptable. We may state parenthetically that clinical experimental evidence indicates that the sympathetic nervous system does not produce Raynaud's disease.[32, 33, 34] However, lumbar sympathectomy uniformly cures Raynaud's disease of the feet, and cervicothoracic sympathectomy cures Raynaud's disease of the hands, or at least, lessens it in a large percentage of cases. Moreover, extensive sympathectomy does reduce the blood pressure of many patients suffering from essential hypertension.[7] The fact that it does not do so routinely does not detract significantly from the observation that it does do so in some cases. Further, it is a common observation that, postoperatively patients experience sharp reduction in their blood pressures and marked acceleration of the rate of the heart when they stand.[7] Studies on the rate of flow of blood through arteries and veins of the extremities before and after extensive sympathectomy show that beyond doubt, this surgical procedure increases the rate of flow of blood.[35] These observations indicate that sympathectomy may modify the mechanism by means of which the blood pressure is elevated in essential hypertension.

Method of Study of Patients Who Have Undergone Extensive Sympathectomy for Essential Hypertension

We have attempted to limit the neurosurgical treatment of hypertension to those patients who have essential hypertension. By careful study we have attempted to exclude patients suffering from primary nephritis, coarctation of the aorta, renal lesions such as atrophic pyelonephritis, Cushing's syndrome and benign pheochromocytoma of the suprarenal glands. The blood pressure of each patient has been determined hourly for 24 consecutive hours, for we are aware of the fallacy of using single determinations of blood pressure as a basis for judging results in such a study. The retina has been examined by an ophthalmologist who is particularly interested in the retinal findings in hypertension. Roentgenologic study of the size of the heart, electrocardiography and tests for renal function have been carried out almost routinely, but we are not reporting the results of these studies because they do not add significantly to the chief considerations, the effects of sympathectomy on blood pressure and on symptoms of hypertension, and because they were usually normal. The response of the blood pressure to immersion of a hand in ice water was determined in almost all instances to

obtain some idea as to the values the blood pressure might attain as a result of nervous stresses and strains. In almost all instances we have determined the reduction of blood pressure resulting from the administration of drugs and also the reduction obtained by rest and sleep. Three grains (0.2 gm.) of sodium amytal has been administered hourly for three successive hours and a 5 per cent solution of pentothal sodium has been injected intravenously until such a time as the blood pressure has not decreased further.[6, 7] All the patients suffering from essential hypertension were classed into groups suggested by Keith, Wagener and Barker because such grouping gives us information about the severity of the hypertension, the effects of elevation of the blood pressure on the arteries, and about the prognosis. We wish to emphasize the fact that this grouping does not indicate the grade of hypertension present, although, usually, the hypertension of patients in each group (except the first, of course) was more severe than that of the preceding group.[11] The essential points of such classification are shown in table 1.

TABLE I

Classification of Essential Hypertension

Group	Degree of Hypertension	Changes in Retinal Arteries	Retinitis	Edema of Optic Disks
1	Mild	Minimal	Absent	Absent
2	Moderate to severe	Moderate	Absent	Absent
3	Moderate to severe	Marked	Present	Absent
4	Severe	Marked	Present	Present

We have attempted to select patients for operation for whom the prospects of significant reduction in blood pressure would be greatest. Unfortunately, much interference with such selection was encountered because we have had to learn by experience which patients were most benefited and which were not, because many patients requested operation even though our studies indicated that they had little chance to benefit from such a procedure and because the best information which we had at the time did not always allow accurate prediction of results. We learned early in this study that it was useless to operate on patients who had congestive heart failure, auricular fibrillation, angina pectoris, significant renal insufficiency or severe hypertensive encephalopathy. In brief, it was evident that little could be accomplished when advanced arterial lesions were present. Albuminuria and slight to moderate enlargement of the heart were not considered contraindications to operation in themselves.

PREOPERATIVE PREDICTION OF EFFECTS OF OPERATION ON BLOOD PRESSURE

Since the blood pressure of some patients is not reduced by sympathectomy, whereas the blood pressure of other patients is greatly reduced by the operation, it is important, preoperatively, to attempt to select the patients

who will be benefited by operation and to refuse operation to those who cannot be benefited. Obviously, in order to influence blood pressure by sympathectomy, elevation of the blood pressure must have been caused by increased resistance of the arterioles, which can be reduced by sympathectomy. If, on the other hand, increased arteriolar resistance is the result of organic changes in the arterioles or of some pressor substance in the blood, sympathectomy would not modify the blood pressure unless it did so in some indirect way, such as by increasing the flow of blood through the kidneys, thus reducing the amount of pressor substance in the blood. To gain useful information, we divided our results, depending upon effect of operation on blood pressure, into three groups: (1) good, (2) fair and (3) temporary and poor. The last-mentioned group included all patients who had died, those who had hemiplegia, those whose blood pressures had returned to the preoperative value after having been reduced for variable periods, and those who had not benefited, even temporarily, from operation. Some patients have been operated on who would not be operated on now, but during much of our earlier experience we were more or less compelled to select patients by the method of trial and error.

As we have indicated previously, there are no methods of predicting results with certainty.[5, 7] However, there is a group of circumstances which indicate that the results of operation on blood pressure will almost certainly be temporary or poor.* These circumstances, in brief, consist of inadequate reduction of blood pressure as a result of such measures as rest, advanced hypertension (group 4) and advanced arterial disease as exemplified by marked sclerosis of the retinal arteries (table 2). We believe that these patients should not be treated by sympathectomy for essential hypertension because the results of operation on blood pressure are almost uniformly disappointing. The more marked the narrowing and sclerosis of the retinal arteries are, the less likely are the results of operation on blood pressure to be good. Thus it is obvious that the results of operation in hypertension, groups 1 and 2, are better than in hypertension, group 3. The response of the systolic and diastolic blood pressures to rest influences results of operation (tables 3 and 4). The more nearly the systolic and diastolic blood pressures approach normal during rest and sleep, the more likely the results are to be good or fair. Unfortunately for accurate prediction, even when the systolic blood pressure has decreased to less than 140 mm. of mercury and the diastolic blood pressure has decreased to 100 mm. of mercury or less as a result of rest, some patients' blood pressures have been reduced only temporarily by operation. Similar results were noted in a study of the value, in predicting results of sympathectomy on blood pressure, of the administration of sodium amytal † and of the injection of pentothal sodium [6]

* Since our studies indicate that the blood pressures of patients who have had results indicated as "fair" react essentially the same as do those who have had results indicated as "good," we have combined the two groups for simplification.

† 3 grains (0.2 gm.) hourly for three successive hours.

TABLE II

Preoperative Prediction of Temporary or Poor Results Based on Studies in Vasodilation and on Observations of the Retinas

	Cases	Temporary or Poor Results, Per Cent
Minimal* diastolic blood pressure		
From rest		
a. More than 110	33	94
b. More than 120	13	100
From injection of pentothal sodium		
a. 105 or more	63	83
b. More than 115	18	90
c. More than 125	7	100
From administration of amytal		
a. 105 or more	31	94
b. 115 or more	10	100
Sclerosis of the retinal arteries, grade 3	17	100
Hypertension, group 4	7	100
Minimal systolic blood pressure resulting from rest		
a. 180 or more	29	93

* The term "minimal" designates the lowest blood pressure resulting from various measures.

TABLE III

A Comparison of the Preoperative Reduction of Systolic Blood Pressure Resulting from Rest in Bed with Results Following Operation

Response of Systolic Blood Pressure to Rest, mm. of Mercury	Cases	Effects of Operation on Blood Pressure	
		Good and Fair, Per Cent	Temporary and Poor, Per Cent
Less than 140	63	48*	52
140–179	128	27	73
180–219	29	7	93

* Indicates lowest blood pressure during rest.

TABLE IV

A Comparison of Preoperative Reduction of Diastolic Blood Pressure Resulting from Rest in Bed with Results Following Operation

Response of Diastolic Blood Pressure to Rest, mm. of Mercury*	Cases	Effects of Operation on Blood Pressure	
		Good and Fair, Per Cent	Temporary and Poor, Per Cent
100 and less	147	37	63
101–110	40	25	75
More than 110	20	6	94

* Indicates lowest blood pressure during rest.

TABLE V

A Comparison of the Preoperative Reduction of Diastolic Blood Pressure Resulting from Administration of Sodium Amytal with the Results Following Operation

Effect of Amytal on Diastolic Blood Pressure, mm. of Mercury	Cases	Effects of Operation on Blood Pressure	
		Good and Fair, Per Cent	Temporary and Poor, Per Cent
Less than 85	32	32	68
Less than 100	106	31	69
101–110	21	10	90
More than 110	11	0	100

on the diastolic blood pressure before operation (table 5). Analyses were made of various other data, such as mean and maximal systolic and diastolic blood pressures, but the results were essentially the same as those reported in the preceding tables (table 6). The conclusions to be drawn from this

TABLE VI

A Comparison of the Preoperative Maximal Diastolic Blood Pressure with the Results Following Operation

Maximal Diastolic Blood Pressure, mm. of Mercury	Cases	Results of Operation on Blood Pressure	
		Good and Fair, Per Cent	Temporary and Poor, Per Cent
Less than 115	26	58	42
115–134	84	33	67
135–154	83	20	80
155 or more	29	28	72

attempt to predict how well extensive sympathectomy will affect blood pressure in essential hypertension may be summarized as follows: The more nearly the blood pressure approaches normal as a result of rest, administration of sodium amytal and the injection of pentothal, and the less marked the vascular disease the more likely extensive sympathectomy is to reduce blood pressure significantly. However, even when responses of blood pressure are adequate and when vascular disease is minimal, extensive sympathectomy may reduce blood pressure only temporarily. When blood pressure is not reduced markedly by rest, administration of sodium amytal and the injection of pentothal sodium, when advanced vascular disease, renal insufficiency or congestive heart failure is present, it is useless to perform extensive sympathectomy for essential hypertension.

Additional factors may be considered when the decision is made as to the advisability of operation. Rapidly progressive hypertension seems to respond less favorably than slowly progressive hypertension does. Generally, patients with very high blood pressures (220 systolic and 130 diastolic or more, expressed in millimeters of mercury) respond unfavorably to sympathectomy. Operation is advisable for patients who have had adequate

medical supervision without benefit, provided clinical studies are satisfactory, whereas patients who have not had adequate medical supervision may be treated medically in order to evaluate the benefit to be derived from such a regime. However, they should not be treated medically for so long that they become unsatisfactory candidates for surgical treatment because of progression of the disease. Naturally, it is desirable to avoid performance of extensive sympathectomy on patients who are ill because of conditions, other than the hypertension, which may be incidental and relatively unimportant. For example, a patient affected by psychoneurosis or nervous exhaustion would not be cured of the condition even if her blood pressure were reduced by sympathectomy.

Rationale of Sympathectomy for Essential Hypertension

The sudden and permanent reduction of high blood pressures following the removal of benign pheochromocytomas from the adrenal gland as well as the frequent occurrence of hypertension among surgeons is responsible for the interest surgeons have taken in the problem of hypertension. The earlier surgical procedures consisted of denervation of the adrenal gland as well as subtotal section of the gland, the operations being based on the principle of attempting to reduce the amount of epinephrine secreted. Inasmuch as epinephrine produces vasoconstriction and inasmuch as extensive sympathectomy is capable of reducing vasoconstriction, surgeons began to speculate as to whether or not it would be possible to develop an operation that might denervate a vascular bed sufficiently large to alter blood pressures in a patient suffering from essential hypertension.[36, 37, 38, 39, 40] Since it has been proved that the peripheral arterial resistance has been reduced and that the flow of blood has been increased by performing extensive sympathectomy in Raynaud's disease, the operation, a bilateral ventral rhizotomy from the sixth thoracic to the second lumbar nerves, was proposed and performed at The Mayo Clinic in 1930. This operation was employed by a number of surgeons who obtained results justifying further investigation of the surgical approach to the problem of essential hypertension.

The operation of ventral rhizotomy [41] was performed on the basis of interrupting sympathetic nerve fibers which left the spinal cord by the way of the ventral roots to join the sympathetic ganglia and trunks before reaching the arterioles. Rhizotomy was extended from the sixth thoracic to the second lumbar nerves so that it would include all the fibers carrying vasomotor impulses through the lower half of the thoracicolumbar sympathetic outflow in order to denervate the blood vessels or to interrupt vasoconstrictor impulses traveling from the central mechanism to the blood vessels supplying the lower half of the body. The operation was also devised to include the sympathetic innervation of the adrenal gland as well as the arterial supply of the kidney with the hope that any sudden dumping of epinephrine might be thereby prevented and that the circulation of the kidney would be in-

creased, thus preventing or minimizing the effects of an anemic kidney which results in the production of renin or angiotonin.

The laminectomy which is necessary to the performance of rhizotomy constituted a formidable procedure, one which was attended by considerable surgical shock. This prompted the development of other surgical technics, less formidable, with the hope of accomplishing the same results as rhizotomy. Inasmuch as subtotal section and denervation of the adrenal gland were of only temporary value in lowering blood pressure, the newer surgical procedures were devised to interrupt splanchnic nerves. The operation developed at The Mayo Clinic in 1935 consisted of resection of the splanchnic nerves with a portion of the celiac ganglion, resection of the upper lumbar sympathetic trunk, including the first and second lumbar ganglia, by a subdiaphragmatic extraperitoneal approach through separate incisions in the lumbar region not unlike those employed for operations on the kidney. Other accepted operations in use today consist of removal of the celiac ganglia as devised by Crile[42] and supradiaphragmatic resection of the splanchnic nerves on both sides as advocated and performed by Peet.[43, 44] Each procedure has its advantages and disadvantages. Since 1935 we have employed the subdiaphragmatic approach because it is attended by a minimum of surgical risk and because it permits the surgeon to include the sympathetic fibers which carry vasomotor impulses to the lumbar sympathetic ganglia. The inclusion of the sympathetic fibers of the lower end of the thoracicolumbar outflow which travel over the two upper white lumbar rami is significant, we believe, since it interrupts the central impulses to the adrenal glands and renal arteries. The operation, unfortunately, does not include those midthoracic fibers that may travel along the aorta and it is very possible that Smithwick's suggestion of combining subdiaphragmatic removal with transdiaphragmatic removal of the splanchnic nerves, with the upper two lumbar ganglia on each side, may prove to be the operative procedure of choice, since it also includes the sympathetic filaments that follow the aorta.

Results of the Postoperative Study

To evaluate the results of (1) subdiaphragmatic resection of the splanchnic nerves, with resection of the celiac ganglion where these fibers enter the ganglion, with (2) resection of the lumbar sympathetic trunk, including the first and second lumbar ganglia on both sides, in the treatment of essential hypertension, we have made every effort possible to have the patients return for reëxamination or to have them submit to reëxamination by their local physician and to have him report on observations of blood pressure as well as to have the patient report on his own observations. This has been done to as late a date as January 1, 1940, a study extending over a period of five years. This includes a series of 300 patients who have submitted to 600 independent operations with no deaths. In one patient, who was con-

valescing from sympathectomy, an acute gangrenous lesion of the gallbladder developed which required an emergency operation, following which pneumonia developed. This patient succumbed, but was the only patient who died following an operative procedure.

In order more accurately to evaluate the results, we have not included thirty patients operated on within the past six months (at the time of writing), because patients almost universally have a pronounced reduction of blood pressure immediately following the operation. We were unable to secure replies to our recent inquiries of thirty-six patients. Ten other patients are not included in the study because splanchnic resection was included with other procedures such as unilateral nephrectomy, or because the operation was performed for patients suffering from hypertension and thromboangiitis obliterans or other accompanying diseases, in which cases it was carried out as an investigative procedure.

The study includes a review of postoperative results in 224 cases. Questionnaires were sent to patients and their physicians unless they had returned to the clinic for reëxamination within three or four months prior to the time that the survey was made. The physicians were asked to fill out a questionnaire on blood pressure studies. The first reading was taken on the patient's entrance to the physician's office, a second reading was taken ten minutes later and a third reading was taken while the patient was standing. The first two readings were made while the patient was reclining and the third was made after the patient had stood in the erect position for one minute. The patients were requested to use the descriptive terms "yes" and "no" about each individual symptom before operation, and the descriptive terms "better," "much better," "slightly better," "unchanged" and "worse," relative to their symptoms at the time they received the questionnaire.

Operative Effects on Blood Pressure

Unless the patient is prepared for operation by the administration of a sedative, such as 3 grains (0.2 gm.) of pentobarbital sodium one hour prior to the administration of the anesthetic agent, the blood pressures will be found at their maximal readings. Occasionally they are so dangerously high that operation must be postponed. But once the patient has become thoroughly anesthetized the blood pressures recede to the preoperative readings made when the patient was at rest in bed. Resection of the splanchnic nerves and the lumbar sympathetic trunk immediately results in recession of blood pressure. The decrease is not so great after a unilateral operation as it is after the second operation which completes resection of the splanchnic nerves and the lumbar sympathetic trunks. Ephedrine is administered in doses of 0.025 gm. and physiologic sodium chloride solution is frequently given intravenously during the second operation in order to prevent surgical shock or complications arising from too excessive decreases in blood pressure. We attempt to maintain a systolic pressure of 100 mm. of mercury.

The pressures will remain below normal for a week, at the end of which period they gradually increase to preoperative values obtaining when the patient was at rest in bed when sodium amytal was administered. All patients experience a marked decrease in blood pressure when they first become ambulatory following their operation. This is accompanied by tachycardia for several months, a phenomenon which we believe is caused by a diminished flow of blood into the heart resulting from the forces of gravity responsible for the accumulation of blood in the denervated vessels which have dilated and acted as reservoirs. This phenomenon is more pronounced in the patient who is free from arterial sclerosis than in the one with definite evidence of beginning sclerosis. Approximately two months following the operation the tachycardia and the excessively low pressures adjust themselves so as not to interfere with the patient's routine.

Postoperative Effects of Sympathectomy on Blood Pressure

The results are summarized in tables 7 and 8. There may be some question as to the classification of the results as "good" or "fair" in some of

Table VII

The Effect of Sympathectomy in Reducing Blood Pressure in the Group of 224 Patients

Postoperative Blood Pressure, Results	Number of Cases	Percentage
Good	27	13
Fair	41	18
Temporary	87	39
Poor*	69	30
Total	224	100

* Includes 34 patients who have died during the five years and 6 who have hemiplegia.

Table VIII

A Comparison of Postoperative Effects on Blood Pressure (in Percentages) Obtained in the Respective Groups of Hypertension in the Group of 224 Patients

Group of Hypertension	Effect of Operation on Blood Pressure*	
	Good and Fair	Temporary and Poor
1 (11 cases)	45	55
2 (137 cases)	33	67
3 (69 cases)	26	74
4 (7 cases)	0	100

* All figures represent percentages.

the instances. We realize that such classification is a matter of opinion. That the reader may judge for himself, we are reporting individual results in the groups indicated as "good" and as "fair" (tables 9 and 10). It

TABLE IX

Effects of Sympathectomy on Blood Pressure (Good Results)

Blood Pressure					
Before Operation			Taken After Operation, Months	After Operation	
Maximal	Minimal	Mean		At Office Examination Only	After 10 Minutes' Rest
240/138	170/105	200/120	43	160/100	150/70
240/158	135/80	180/120	41	160/100	170/110
250/160	182/98	210/129	37	150/100	130/80
160/110	136/86	150/100	32	120/84	116/80
220/140	122/80	170/110	30	170/90	160/80
192/130	130/90	150/105	30	164/84	148/72
230/126	150/100	175/115	30	166/88	164/86
224/140	170/112	190/120	28	170/80	164/78
164/114	130/50	140/80	27	138/82	132/80
230/150	188/108		27	142/85	126/85
228/160	150/110	185/135	25	140/108	134/98
214/160	160/110	170/110	19	142/86	160/100
145/110	85/60	120/80	13	136/84	120/76
160/110	140/90	150/100	12	140/90	
190/130	136/96	150/115	10	135/85	
195/130	150/95	170/115	9	152/98	122/98
200/120	130/90	180/110	7	118/90	116/84
150/100	132/90		7	138/92	132/85
240/100	130/90	150/100	7	150/82	132/80
200/120	150/110	170/114	6	130/80	124/80
220/140	140/94	170/120	6	164/90	158/90
210/120	120/80	150/90	6	154/92	138/78
174/120	138/95	160/110	5	140/100	120/80
220/128	155/90	190/110	3	145/100	
200/144	135/100	170/110	3	130/86	120/84
210/155	176/110	190/135	3	150/108	
200/115		140/95	3	162/92	144/84

seems fair to compare "maximal" pressures determined at The Mayo Clinic with the pressures determined by the patients' physicians when they first came into the physicians' offices, for at the clinic the "maximal" pressures were almost always those determined at the time of the original examination. However, the "minimal" pressures determined at the clinic do not correspond to the pressures determined at the referring physician's office after ten minutes of rest on the part of the patient. The "minimal" pressures determined by us were the lowest pressures occurring during 24 hours of rest and sleep, and naturally they would be considerably lower than if the rest period had been only ten minutes. Some of the results which we have listed as "fair" might be considered "poor" by other observers, but some of them might also be considered good. The designation "temporary and poor" includes those patients whose blood pressures were as high at the time of our last study as they had been before operation. They are not designated "poor" alone because many of the patients included in this group had experienced marked reduction in blood pressures for many months after

operation. Even temporary reduction of blood pressure of several months should increase expectancy of life and delay disastrous arterial changes.

The effect of sympathectomy on the permanent reduction of blood pressures is somewhat disappointing. However, the effect is approximately that

TABLE X

Effects of Sympathectomy on Blood Pressure (Fair Results)

Blood Pressure					
Before Operation			Taken After Operation, Months	After Operation	
Maximal	Minimal	Mean		At Office Examination Only	After 10 Minutes' Rest
210/124	140/100	170/110	55	180/110	170/110
235/125	130/85	180/105	50	200/110	190/110
200/130	145/90	170/100	49	188/105	175/100
204/140	145/100	170/110	48	155/110	155/110
220/150	170/120	190/130	47	160/116	154/112
220/120	140/100	180/110	46	178/105	172/105
228/142	170/108	190/120	40	190/108	220/120
168/92	132/90	150/100	36	158/100	
200/135	148/110	140/94	35	146/108	130/98
234/142	142/102	165/113	35	184/106	176/112
180/110	140/95	145/100	30	176/100	152/108
170/118	110/70	135/90	30	160/108	154/106
220/140	156/92	188/136	30	170/110	160/108
198/126	144/90	160/100	29	195/100	180/100
235/140	156/100	195/120	29	155/108	158/110
220/114	170/98	190/110	27	174/96	172/92
184/118	120/85	130/90	27	160/100	152/98
220/110	170/100	190/110	26	185/105	180/100
290/120	120/75	150/100	26	152/104	143/104
185/110	110/70	140/95	25	170/98	170/98
220/90	164/86		24	160/110	160/105
210/140	110/95		24	190/110	162/100
170/120	120/70		24	180/96	136/90
210/140	150/100	170/120	23	142/120	150/100
170/120	125/80	145/95	23	180/96	
218/140	160/100	170/110	19	190/100	160/100
190/120	136/100	160/110	17	158/100	140/100
210/168	130/80	168/128	17	150/110	150/100
220/120	140/94	160/110	15	168/108	170/110
160/110	132/80	145/90	14	150/100	
220/160	138/96	150/110	12	156/108	
185/115	135/85	155/100	9	160/104	140/100
200/120	145/90	173/110	8	156/100	148/96
190/100	135/90		7	146/102	118/94
220/160	160/105	180/120	5	170/110	150/110
190/110	140/90	150/100	5	170/100	170/100
230/130	140/80		4	186/108	
200/130	150/100	175/115	4	180/110	168/106
195/120	120/65	160/105	3	160/100	
204/140	130/90	160/110	3	180/116	174/116
190/120	160/94	170/100	3	200/96	164/96

which earlier experience taught us to expect. The results which we have reported might be considered excellent if they concerned, for instance, the surgical treatment of cancer. When they are considered in relation to hyper-

tension, it is well to bear in mind the fact that hypertension is as deadly as cancer. The relief or amelioration of symptoms with the extension of the expectancy of life in the patients in advanced group may justify the surgical procedure, since many patients continue to experience clinical relief and are able to return to a gainful occupation even though blood pressure values have failed to remain normal.

Postoperative Effects of Sympathectomy on the Clinical Symptoms

Although it is disappointing to see blood pressures return to preoperative values in patients, it is gratifying to see many of these patients remain free from clinical symptoms. The only explanation that we can give for the fact that patients had been free from symptoms even though preoperative pressure levels have returned is that the maximum pressures have not been reached, the so-called maximum ceiling of pressure has remained lower than before operation. It may also be due to a narrowing of systolic and diastolic range following operation. We are aware that internists have said that any active treatment is effective for a time in relieving symptoms and we grant that this might be true in early instances of the disease or instances in which the treatment includes forced rest in bed. Our experience has revealed that the patient who has a progressive disease will soon have a return of his symptoms. Therefore the increased relief of symptoms obtained by sympathectomy probably warrants performance of the operation occasionally in the patient whose condition is " borderline " and who does not respond to pre-

Table XI

Relief of Clinical Symptoms by Sympathectomy According to the Effects Produced on Blood

Postoperative Blood Pressure, Results	Headache			Dizziness			Tiredness			Thoracic Pain			Shortness Breath		
	Number of Cases			Number of Cases			Number of Cases			Number of Cases			Number of Cases		
	Better	Unchanged and Worse	New*	Better	Unchanged and Worse	New*	Better	Unchanged and Worse	New*	Better	Unchanged and Worse	New*	Better	Unchanged and Worse	New*
Good	15	1	0	12	0	2	10	7	1	6	1	1	10	4	5
Fair	28	1	0	17	3	1	13	10	1	7	4	3	12	8	5
Temporary or poor	67	18	4	56	5	4	53	36	8	20	14	12	37	32	12

* This designation applies to symptoms noted only since operation.

operative vasodilating measures. Table 11 includes data from preoperative histories and replies to an examination or questionnaire. We again have tried to compare the clinical results with postoperative results in blood pressure. A review of table 11 shows in one line that although the reductions in

blood pressure have been temporary or poor the clinical relief has continued. Table 12 represents a summary of clinical relief obtained.

TABLE XII

Relief of Clinical Symptoms by Sympathectomy: Percentages Are Obtained by Comparing Preoperative and Postoperative Data

Postoperative Blood Pressure, Results	Headache	Dizziness	Tiredness	Thoracic Pain	Shortness Breath
	Percentage of Cases in Which Relief Was Obtained				
Good and fair	94	90	58	72	65
Temporary and poor*	79	92	60	59	54

* Relief of symptoms at time when blood pressure had returned to preoperative value.

SEQUELAE

Our recent studies of the sequelae following sympathectomy for essential hypertension are not unlike those previously reported, and therefore we will not review them at this time.[45]

CONCLUSIONS

1. The results of operation for essential hypertension can be predicted with reasonable certainty by observing the response of the blood pressure to rest and sleep, to the ingestion of sodium amytal and to the intravenous injection of pentothal sodium. When poor results of operation are predicted as a result of these tests, the results are almost uniformly unfavorable. When good results are predicted, some patients do not receive as much benefit from operation as was anticipated.

2. There have been no operative deaths in a series of 300 cases. The operation itself does not disable, although anhidrosis of the lower extremities and loss of ejaculation and probably of fertility of the male patient result. Female patients have borne children following the operation.

3. Clinical symptoms invariably disappear with reduction of blood pressure, but in a number of instances the patient continues to be free from symptoms even though there has been a gradual return of elevated blood pressures.

4. Our experiences justify continuance of the operation in the treatment of essential hypertension. The individuals who will receive the most benefit from surgical treatment are those who seek treatment early in the course of their progressive disease, before irreparable damage has resulted to the cardiorenal vascular tissues.

REFERENCES

1. ADSON, A. W., and ALLEN, E. V.: Essential hypertension; general considerations and report of results of treatment by extensive resection of sympathetic nerves and partial resection of both suprarenal glands, Proc. Internat. Assemb. Inter-State Post-Grad. Med. Assoc. North Am., 1936, 181–191.

2. ADSON, A. W., and ALLEN, E. V.: Essential hypertension. I. General considerations. II. The rationale and methods of surgical treatment. III. Selection of patients for and results of surgical treatment, Proc. Staff Meet., Mayo Clin., 1937, xii, 1–4; 49–52; 75–78.
3. ADSON, A. W., CRAIG, W. McK., and BROWN, G. E.: Surgery in its relation to hypertension, Surg., Gynec. and Obst., 1936, lxii, 314–331.
4. ALLEN, E. V., and ADSON, A. W.: Comments on the surgical treatment of essential hypertension, Proc. Staff Meet., Mayo Clin., 1937, xii, 588–591.
5. ALLEN, E. V., and ADSON, A. W.: The physiological effects of extensive sympathectomy for essential hypertension, Am. Heart Jr., 1937, xiv, 415–427.
6. ALLEN, E. V., LUNDY, J. S., and ADSON, A. W.: Preoperative prediction of effects on blood pressure of neurosurgical treatment of hypertension, Proc. Staff Meet., Mayo Clin., 1936, xi, 401–406.
7. ALLEN, E. V., and ADSON, A. W.: Physiologic effects of extensive sympathectomy for essential hypertension; further observations, ANN. INT. MED., 1938, xi, 2151–2171.
8. BARKER, M. H.: Symposium on nephritis; the use of cyanates in the treatment of hypertension, Wisconsin Med. Jr., 1937, xxxvi, 28–32.
9. FAHR, GEORGE: Hypertension heart, Am. Jr. Med. Sci., 1928, clxxv, 453–472.
10. FISHBERG, A. M.: Hypertension and nephritis, Ed. 4, 1939, Lea and Febiger, Philadelphia.
11. KEITH, N. M., WAGENER, H. P., and BARKER, N. W.: Some different types of essential hypertension; their course and prognosis, Am. Jr. Med. Sci., 1939, cxcvii, 332–343.
12. ALLEN, E. V.: Disease of blood vessels and lymph vessels and abnormalities of blood pressure. *In* MUSSER, J. H.: Internal Medicine; its theory and practice in contributions by American authors, Ed. 3, 1938, Lea and Febiger, Philadelphia.
13. DALEY, R. M.: The health of the executive; a modern problem, Proc. Occupation Disease Symposium, Northwestern University Medical School, 1938.
14. GOLDBLATT, HARRY: Studies on experimental hypertension. V. The pathogenesis of experimental hypertension due to renal ischemia, ANN. INT. MED., 1937, xi, 69–103.
15. BROWN, G. E.: Daily and monthly rhythm in blood pressure of a man with hypertension; a three-year study, ANN. INT. MED., 1930, iii, 1177–1189.
16. MUELLER, SELMA C., and BROWN, G. E.: Hourly rhythms in blood pressure in persons with normal and elevated pressures, ANN. INT. MED., 1930, iii, 1190–1200.
17. ALLEN, E. V., and HINES, E. A., JR.: Fluctuations of blood pressure, Modern Concepts of Cardiovascular Disease, Vol. 8, no. 11, 1939.
18. STIEGLITZ, E. J.: Bismuth subnitrate in the treatment of arterial hypertension, Jr. Am. Med. Assoc., 1930, xcv, 842–846.
19. AYMAN, DAVID: Bismuth subnitrate in the treatment of arteriolar (essential) hypertension, Jr. Am. Med. Assoc., 1932, xcviii, 545–548.
20. LOGEFEIL, R. C.: Observations on the use of potassium sulphocyanate (rhodan) in the treatment of essential hypertension, Minnesota Med., 1929, xii, 151–159.
21. AYMAN, DAVID: Potassium thiocyanate in the treatment of essential hypertension; its impracticability, Jr. Am. Med. Assoc., 1931, xcvi, 1852–1857.
22. BARKER, M. H.: The blood cyanates in the treatment of hypertension, Jr. Am. Med. Assoc., 1936, cvi, 762–767.
23. GRIFFITH, J. Q., JR., and LINDAUER, M. A.: Thiocyanate therapy in hypertension including a new micromethod for determining blood thiocyanates, Am. Heart Jr., 1937, xiv, 710–716.
24. WALD, M. H., LINDBERG, H. A., and BARKER, M. H.: The toxic manifestations of the thiocyanates, Jr. Am. Med. Assoc., 1939, cxii, 1120–1124.
25. DAVIS, LOYAL, and BARKER, M. H.: Clinical and experimental experiences in the surgical treatment of hypertension, Ann. Surg., 1939, cx, 1016–1036.
26. AYMAN, DAVID: An evaluation of therapeutic results in essential hypertension; the interpretation of symptomatic relief, Jr. Am. Med. Assoc., 1930, xcv, 246–249.

27. Elliott, A. R.: The treatment of high blood pressure, Jr. Am. Med. Assoc., 1915, lxv, 999–1002.
28. Moschcowitz, Eli: The treatment of hypertension, Am. Jr. Med. Sci., 1920, clix, 517–524.
29. Prinzmetal, M., and Wilson, C.: Nature of peripheral resistance in arterial hypertension with special reference to vasomotor system, Jr. Clin. Invest., 1936, xv, 63–83.
30. Pickering, G. W.: Peripheral resistance in persistent arterial hypertension, Clin. Sci., 1936, ii, 209–235.
31. Stead, E. A., Jr., and Kunkel, Paul: Nature of peripheral resistance in arterial hypertension, Jr. Clin. Invest., 1940, xix, 25–34.
32. Lewis, Thomas: Experiments relating to the peripheral mechanism involved in spasmodic arrest of the circulation in the fingers, a variety of Raynaud's disease, Heart, 1929, xv, 7–101.
33. Lewis, Thomas: Observations upon the reactions of the vessels of the human skin to cold, Heart, 1930, xv, 177–208.
34. Simpson, S. L., Brown, G. E., and Adson, A. W.: Raynaud's disease; evidence that it is a type of vasomotor neurosis, Arch. Neurol. and Psychiat., 1931, xxvi, 687–718.
35. Kvale, W. F., Smith, L. A., and Allen, E. V.: Speed of blood flow in the arteries and in the veins of man, Arch. Surg., 1940, xl, 344–351.
36. Anderson, I. G.: The surgical treatment of essential hypertension, Jr. Clin. Med., 1939, iv, 1–25.
37. Fasciolo, J. C.: Hipertensión arterial nefrógena; estudio experimental, Buenos Aires, Editor "El Ateneo," 1939, 161 pp.
38. Flothow, P. G.: The surgical treatment of essential hypertension, Am. Jr. Surg., 1939, xliv, 535–543.
39. Page, I. H.: The production of persistent arterial hypertension by cellophane perinephritis, Jr. Am. Med. Assoc., 1939, cxiii, 2046–2048.
40. Page, I. H., and Helmer, O. M.: A crystalline pressor substance (angiotonin) resulting from the reaction between renin and renin-activator, Jr. Exper. Med., 1940, lxxi, 29–42.
41. Adson, A. W., and Brown, G. E.: Malignant hypertension; report of case treated by bilateral section of anterior spinal nerve roots from the sixth thoracic to the second lumbar, inclusive, Jr. Am. Med. Assoc., 1934, cii, 1115–1118.
42. Crile, George and Crile, George, Jr.: Blood pressure changes in essential hypertension after excision of the celiac ganglion and denervation of the aortic plexus, Cleveland Clin. Quart., 1936, iii, 268–277.
43. Peet, M. M.: The surgical treatment of hypertension, Jr. Internat. de Chir., 1940, v, 1–40.
44. Freyberg, R. H., and Peet, M. M.: The effect on the kidney of bilateral splanchnicectomy in patients with hypertension, Jr. Clin. Invest., 1937, xvi, 49–65.
45. Allen, E. V., and Adson, A. W.: The physiologic effects of extensive sympathectomy for essential hypertension, Am. Heart Jr., 1937, xiv, 415–427.

THE ACTIVITIES OF THE AMERICAN COLLEGE OF PHYSICIANS IN GRADUATE MEDICAL EDUCATION *

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DURING recent years interest in graduate medical education has increased steadily. Practitioners in the clinical branches recognize the fact that medical knowledge changes and that methods of practice should change also and with as little lag in application as possible. Thus the demand from practitioners for opportunity and guidance, in what Bruce has aptly called continuation study. Moreover, current graduates in Medicine no longer consider their education completed when the medical degree is conferred. Medical education and training for medical practice, whether the latter be general or confined to a special field, are recognized as continuing processes. Reflections of this point of view are to be found in the activities of some of the medical schools, but more conspicuously perhaps in the activities of organizations composed of practicing physicians and surgeons. Let us examine briefly some of the factors responsible for the current interest in extending the medical graduates' instruction beyond the formal courses prescribed by the medical schools.

Certainly one factor in producing the increased demand for graduate medical training resides in the superior quality of the recent graduates of medical schools. The care exercised by the schools in selecting students for admission results, undoubtedly, in improving the quality of the graduates. These graduates are mature men and women who have completed successfully a carefully planned and executed educational program in a highly competitive field. It is not surprising that individuals of this type recognize the importance of supplementing the basic knowledge acquired in the medical school by practical, vocational training in hospitals to the end of developing competency in practice. Hence, the medical school graduate now invariably includes hospital training in his program of organized medical instruction. Moreover, medical school faculties no longer consider that the instruction afforded students by the medical school is sufficient in itself to qualify graduates for practice. Some faculties have developed the philosophy that the university medical school is concerned primarily with providing a basic medical education, which the student may utilize in medical practice, medical research or simply as an educational discipline. Many medical educators state that they no longer attempt to provide medical students with vocational training. This responsibility, it is pointed out, is assumed by other agencies. The medical schools of the future, one dean states, will place even more emphasis upon basic medical education and less upon vocational train-

* Read at the Cleveland meeting of the American College of Physicians April 1, 1940.

ing. "The basic medical course is the doorway through which men pass to all the fields of Medicine. It constitutes the most powerful influence tending to unite the varied fields of medical work." * The emphasis here is certainly not upon vocational or professional training. The university, according to this concept, has no obligation to the public regarding the technical fitness of its graduates for practice. Thus the graduates look elsewhere for vocational or practical training. Those graduates who aspire to practice are deeply concerned with this. They demand graduate or vocational training in the form of hospital staff positions.

Medical graduates are influenced by other agencies than their schools to acquire graduate training. Among these are the state and national boards of medical examiners. These boards, by their requirements for licensure or approval, emphasize the importance of graduate training. The national board and many of the state boards will not accept as candidates for examination medical graduates who have not had at least one year of graduate training as hospital interns. This requirement doubtless acts as an incentive to many students to acquire even more extensive training. If "at least one year" is required, does this not indicate the boards' opinion that two or three or more are desirable? Certainly more extensive training is desirable if the students aspire to any type of specialized practice. The requirements of the American certification boards dispel all doubt regarding this point.

The attitude of the general public also creates demand for graduate training for practitioners. All types of health service, public and private, are undergoing close scrutiny by the layman. Medical news is no longer found exclusively in professional journals. The public is deeply interested in medical news, scientific or otherwise. The daily and weekly newsorgans attempt to satisfy the demand. Moreover, the layman knows where his young doctor graduated in Medicine and where he served his internship and whether he continues to keep abreast by attendance on medical meetings, postgraduate assemblies, formal courses for continuation study, etc. The doctor is not a person set apart in the community and accepted uncritically because M.D. appears after his name.

More important than any other factor in creating the demand for adequate graduate training is the desire of the profession to elevate the standards of medical practice. The contribution of the American Medical Association in the field of medical education, through its Council on Medical Education and Hospitals, should be a source of pride to every member. Its most outstanding work has been in undergraduate medical education. The American Medical Association has played a conspicuous rôle in the evolution of medical education in this country. I believe that the medical schools of the United States are superior to those of any country in the world. The educational requirements for admission to these schools, the content of the curricula, the facilities for laboratory and clinical study have been made the subject of review and evaluation by the Council on Medical Education and Hospitals.

* Dr. C. Sidney Burwell, Dean, Harvard Medical School.

The influence of this Council is an expression of the influence of the membership of the American Medical Association. It operates under no other authorization; its enforcement or disciplinary power resides solely in the strength of the medical opinion it represents. Current medical opinion regarding the desirability of graduate training and continuation study for physicians is unmistakably affirmative.

As specialization in medical practice evolved, special societies came into existence. The American College of Physicians is composed of some 4000 individuals especially interested in Internal Medicine and the medical specialties. One of the stated objectives of this College is to maintain and advance the highest possible standards in medical education, medical practice and medical research . . . to maintain the dignity and efficiency of Internal Medicine in its relation to public welfare. The efforts of our organization to attain these objectives are represented by (1) the annual meetings—postgraduate assemblies; (2) the provision of research fellowships; (3) the publication of the *Annals of Internal Medicine;* and (4) the sponsorship of continuing professional education in the form of graduate courses in Medicine.

Membership in the College is contingent upon certain requirements over and above graduation from an approved medical school. Among others there is a requirement regarding graduate training. The graduate of the medical school who aspires to membership in the College must avail himself of graduate training. The American College of Physicians and the section on Medicine of the American Medical Association sponsored the creation of the American Board of Internal Medicine. This Board, made up of representatives from the Section on Medicine of the American Medical Association and the American College of Physicians, certifies as to the competency of candidates appearing before it to practice Internal Medicine as a specialty. This Board requires that, to be eligible for certification, candidates must have adequate training.

Thus, the American College of Physicians, through its requirements for admission, and the American Board of Internal Medicine, through its eligibility requirements, stimulate graduates of medical schools who plan careers in Internal Medicine to seek graduate training. The Board of Regents of the College has recognized the obligation it assumed in thus creating additional demands for graduate training in Internal Medicine. To the end of meeting this obligation, in part at least, it set about in 1938 to determine how it could improve the training obtained by the hospital intern, assistant resident and resident in Medicine. The American Board of Internal Medicine feels also that, in this field of graduate training, it has interests and obligations. In approaching the problem the College and the American Board were impressed immediately by the importance of the work which the Council on Medical Education and Hospitals of the American Medical Association initiated in 1936, when it began its survey of hospitals to determine their fitness for special training in the specialties. Moreover, our Regents were cognizant of the contribution which the College of Surgeons makes in its

annual survey of the facilities for hospital training for Surgery and the surgical specialties and considered that the College of Surgeons by its very nature was preëminently qualified to determine standards for surgical internships and residencies and to evaluate hospital positions on the basis of these standards. Thus, it appeared to the Regents that the American College of Physicians could assay to render its contribution to the problem of graduate training for internists either in coöperation with one of the two organizations already in the field or as an independent enterprise. Invitations were extended us by both the American College of Surgeons and the Council on Medical Education and Hospitals of the American Medical Association to relate our interests to theirs. After much deliberation the Regents concluded that it would be unwise for the College to make its contribution either independently or as a coöperative enterprise with the American College of Surgeons, since in either instance it would duplicate work already started by the Council on Medical Education and Hospitals of the American Medical Association. Moreover, it was apparent that the interests of the American Board of Internal Medicine also were concerned in the matter. Therefore, an effort was made, at the invitation of the Council on Medical Education and Hospitals of the American Medical Association, to evolve a plan by which the Council, the College and the American Board could coördinate interests in a mutual undertaking. Tentative proposals, regarding the organization of a Conference Committee, were submitted by representatives of the three bodies concerned. It is hoped that by means of this Committee, the American College of Physicians and the American Board of Internal Medicine can participate in the work of the Council in surveying residencies, assistant residencies, internships and fellowships in Medicine, utilizing the existing machinery of the Council. The memorandum on the organization of of this *Conference Committee* of the Council on Medical Education and Hospitals of the American Medical Association follows. It has been approved by the Board of Regents of the College, the American Board of Internal Medicine, and the Council on Medical Education and Hospitals of the American Medical Association.

The Proposal for Establishing a Conference Committee Concerned with Graduate Training in the Field of Internal Medicine

1. It is proposed that there be created a Conference Committee on Graduate Training in Medicine.

2. The Conference Committee shall consist of two delegates from each of the following organizations: The American College of Physicians, the American Board of Internal Medicine, and the Council on Medical Education and Hospitals of the American Medical Association.

3. The function of the Conference Committee on Graduate Training in Medicine shall be:

(*a*) To submit observations and recommendations which may be useful in furthering the purposes of the constituent organizations.

(*b*) To consider those elements which are regarded as essential in the appraisal of residencies, fellowships and systematic graduate courses for which the approval of the constituent organizations may be sought.

4. Actual visitation of medical schools and hospitals for the purpose of securing information regarding standards and facilities for instruction in Internal Medicine shall in general be made by the staff of the Council on Medical Education and Hospitals; the Council will, however, welcome the assistance of qualified representatives of the College and the Board when such assistance is available. Information thus obtained shall be made regularly available to the Conference Committee.

5. Residencies, fellowships or systematic courses in the field of Internal Medicine will be considered by the Conference Committee before independent action is taken by any one of the constituent organizations.

While the foregoing memorandum covers the situation as far as the Committee understands the matter delegated to it, it is the feeling of the Committee that it may well be desirable to include members of other medical specialty boards in a conference pertaining to the problems of graduate training.

The Conference Committee, which is proposed in this memorandum, has been created. It should make it possible for the College and the American Board of Internal Medicine to participate in the definition of the standards by which Council field workers evaluate medical internships, residencies, fellowships, etc. Moreover, the Conference Committee will have the opportunity to review the results of the field work and to make recommendations to the Council on Medical Education and Hospitals relative to its approval or disapproval of medical internships, residencies, fellowships, etc.

The Conference Committee has held its organization meeting and there is good reason to believe that through it the College will be influential in determining the quality and number of internships, residencies, and fellowships available for graduate training in Medicine. This contribution by the College to graduate education in Internal Medicine will be related in a natural, logical way to the traditional functions of the Council on Medical Education and Hospitals of the American Medical Association and to the interests of the American Board of Internal Medicine. If the objectives of the Conference Committee on Internal Medicine are attained, this method of cooperative work with the Council on Medical Education and Hospitals of the American Medical Association may be employed by other special societies and certification boards.

The Regents and Governors of the American College of Physicians and the Committee on Postgraduate Education have considered other means by which the College may create or improve facilities for special training in Medicine. Topics which have been considered in this connection are: (1)

the sponsorship of regional meetings of the College featuring educational programs in those sections of the country where this seems indicated; (2) the production of talking picture clinics and demonstrations for use at the regional meetings; (3) the establishment of American College of Physicians Fellowships at carefully selected medical schools and hospitals to the end of increasing the number of desirable positions available to recent graduates for graduate training in Internal Medicine and the basic medical sciences. A thoughtful consideration of this program by the Fellows is coveted by the Board of Regents, the Governors, and the Committee on Postgraduate Education. Certainly the College can make no more important contribution to the American public and the medical profession than by providing ways and means for men to increase their knowledge of and competency in Internal Medicine.

CASE REPORTS

THE CLINICAL ASPECTS OF CARDIAC INVOLVEMENT (RIGHT AURICULAR TUMOR) IN IDIOPATHIC HEMORRHAGIC SARCOMA (KAPOSI'S DISEASE) *

By G. Louis Weller, Jr., M.D., F.A.C.P., *Washington, D. C.*

Primary involvement of the heart in Kaposi's disease never has been reported as such, insofar as can be determined. That cases of this type have occurred, however, is evident from the study of the original tissue. This type of involvement is suggested when the histological description of a cardiac neoplasm is characterized by sarcomatous tissue infiltrated with much hemorrhage. The two cases of this type which form the basis of this report were diagnosed as Kaposi's disease at autopsy.

Both cases have presented similar, and at the same time unusual clinical pictures. The first case presented all, and the second case presented many of the characteristics necessary for antemortem diagnosis. Although these tumors admittedly are rare, their clinical diagnosis is of interest.

In the two cases here reported, the clinical syndrome, supported by postmortem findings which were almost identical in the two cases, seems definite enough to warrant its establishment as a distinct entity. The present paper analyzes the features of the cases reported here and of similar cases in the literature.

Literature

Cases of the type discussed in this paper are reported in adequate enough numbers in the literature to present an interesting background for the present cases. Raw,[1] in 1898, reports the case of a 43 year old charwoman who experienced pain in the chest, dyspnea upon exertion and who "had to sit up in bed at night three and one-half years before admission" even though she was able to do a little work until two months before admission. Admitted to hospital because of marked pain in the right chest, upon examination she was found to have an anxious expression, orthopnea, and marked dyspnea of a spasmodic character. Ascites, edema of the legs, enlargement of superficial veins of the thorax, dullness of the right chest and enlargement of the liver also were present. At autopsy a tear was found in the inferior vena cava just before its entrance into the right auricle, and a large, hard sarcomatous tumor, three by three inches, was present in the right auricle. This growth extended directly down the course of the inferior vena cava and terminated on the under surface of the liver as distinct hard nodular masses.

Norton's patient,[2] a 29 year old white male, was taken ill two days before admission to the hospital, with cough and bloody sputum which became rusty on

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the next day. There was moderate cyanosis, but examination of the heart revealed no especial abnormalities. While hospitalized the patient improved during the first week, but later became confused, morose and then delirious. The tumor in this instance was a large one filling the entire left auricle and extending down into the mitral orifice. The histological characteristics, from the description, were those of Kaposi's sarcoma.

A third patient, reported as a Cabot Case and discussed by Drs. Breed, Sanderson, Mallory and Holmes [3] was a 33 year old white female. During the two years preceding admission to hospital the patient had suffered attacks of substernal oppression and breathlessness. Seven months before admission cough, fever, and chest pains appeared. No hemoptysis was noted, but the dyspnea increased to such an extent that the patient was bedfast most of the time. Roentgen-ray examinations prior to one week before admission were negative, while the one taken at that time showed a lobulated mass in the region of the right auricle. Histological examination of the tumor, both as is reported in the literature, and as is agreed upon following interchange of sections with Dr. Mallory, shows the tumor to be a Kaposi sarcoma.

Clerc and Colleagues' patient,[4] a 34 year old white female, likewise presented the symptoms noted above. Binder [5] reports a case of tumor of the right auricle in which edema, beginning originally in the face and then spreading downwards, was a prominent feature. Ehrenberg [6] reports similar clinical findings in his case.

Bordley [7] reports the following clinical syndrome associated with myxoma of the left auricle. Onset is characterized by palpitation, dyspnea upon exertion, and weakness. These episodes at first occur about one week apart, and after awhile are a constant accompaniment of exertion. Later orthopnea and paroxysms of cough, together with other signs of left heart failure, appear. There is no response to rest or digitalis.

Case Reports

Case 1. V. M., a 30 year old white male, was seen first on November 28, 1937. A month prior to that time he had developed what to him appeared to be a cold and bronchitis, characterized by cough, yellowish sputum and night sweats. On December 14, 1937, he became nauseated and vomited. At this time, also, he first noted swelling of the entire face and neck. This swelling was worse in the morning upon awakening and disappeared towards evening. It was noted upon examination at this time that the blood pressure was normal, that cardiac size, rate, rhythm and sounds were normal, and that the lungs were clear to percussion and auscultation. Mild jaundice of the skin and sclerae was present. The liver was enlarged to three fingers'-breadth below the costal margin.

Following a diagnosis by his local physician of gall-bladder trouble the patient was given intramuscular injections of calcium gluconate on alternate days over a period of about a week. Although the injections seemed to decrease the amount of swelling temporarily, towards the end of the period of injections the face had become increasingly swelled. This facial edema disappeared after the patient was up and about. Temperature at this time reached a maximum of 101° F. The liver remained palpable, and there was tenderness in the region of the gall-bladder. A flat plate of the abdomen showed no evidence of gall stones, but revealed that the right lobe of the liver was enlarged to the crest of the ilium. Erythrocyte count on November 29 was 3.8 millions of cells, leukocytes 9.3 thousands, and hemoglobin 65 per cent.

During the next several weeks the patient continued to cough frequently, the cough being very distressing and appearing chiefly at night. Night sweats were frequent and marked.

On December 27, 1927, the patient was admitted to the George Washington University Hospital. Here his temperature was found to range from 101° F., to 102° F., maximum. He was constantly orthopneic. Twenty-four hours after admission there was epistaxis followed 24 hours later by slight hemoptysis.

A roentgen-ray examination of the chest revealed marked enlargement of the pericardial sac both to right and left. Within the right half of the cardiac shadow was a vertical shadow in the region of the right auricle, the nature of which, however, was not obvious. A six-foot film with the patient in the prone position showed marked widening of the cardiac shadow at the base.

Upon aspiration of the pericardium December 29, 1937, 3 c.c. of a bloody serous fluid were removed. After centrifuging, the erythrocytes formed a shallow layer in the bottom of the test tube. The supernatant fluid was clear and xanthochromic. No bacteria were visible in gram-stained sections. In a Wright-stained film erythrocytes predominated. The few leukocytes present were approximately 75 per cent lymphocytes and 25 per cent polymorphonuclear cells.

Fifteen hours following the first pericardial tap, the patient meanwhile having continued orthopneic and uncomfortable, a second pericardial tap was done. On this latter occasion, three hours before death, 700 c.c. of a bloody serous fluid were removed. Prior to tapping the patient's blood pressure was 120 systolic and 110 diastolic and he complained of severe pressure upon the anterior chest. Following removal of the pericardial fluid the blood pressure was practically unobtainable, only an occasional sound being audible between 80 and 70 millimeters of pressure. During the early period of the paracentesis the patient's respiration improved considerably, but as the aspiration continued he passed slowly into a condition of shock, becoming unconscious, and perspiring profusely. He became gradually more dyspneic, orthopneic, and very cyanotic, with no pulse obtainable at the wrist. He died suddenly two hours after the paracentesis.

Autopsy done four hours after death showed the following: The body was that of a well nourished male. Lips and gums were cyanotic. The neck was full. The vessels of the neck stood out prominently. About 1000 c.c. of amber colored fluid were present upon opening the abdominal cavity. The abdominal organs showed evidences of chronic passive congestion. The spleen was slightly enlarged, weighing 190 grams. Both kidneys were of normal size and appeared congested. The liver weighed 1850 grams and upon cut surface showed marked mottling from yellow to purplish red. The gall-bladder contained no stones and bile escaped freely through the bile ducts.

The left pleural cavity contained about 800 c.c. of blood-tinged fluid. The left lung was almost completely collapsed, presenting numerous areas of atelectasis and a few small infarcts in the lower lobes, mostly near the periphery. The remaining lung tissue showed chronic passive congestion. Practically all of the branches of the pulmonary artery were occluded by thrombi.

The right pleural cavity contained about 1000 c.c. of blood-tinged fluid and the right lung presented changes identical with those in the left lung.

The pericardial cavity was markedly dilated and contained approximately 900 c.c. of bloody fluid. The heart (figure 1) was enlarged, especially the right auricle, which occupied almost the entire anterior surface and measured 10 by 12 cm. in diameter. The heart weighed 725 grams. The pericardial surface of the right auricle was hemorrhagic and markedly roughened. The right auricle was almost completely occluded by a large mass firmly attached to the wall. The tumor was very hard and cut with marked resistance. The peripheral portion of the tumor, upon section, was

hemorrhagic while the central portion was whitish and flesh-like in appearance. The endothelial surface of the tumor was smooth. The tumor was seen to impinge upon the entrance of the vena cava into the auricle and also occluded the tricuspid orifice, the leaflets of which were thin and smooth. The right ventricle, left auricle, and left

FIG. 1. Heart with tumor in right auricle, first case.

ventricle showed no significant abnormality. Microscopic examination of the lung showed marked congestion of the blood vessels with extravasation of blood in several small areas. Pulmonary edema was seen in some regions as was hemorrhagic effusion into the alveoli. There were thrombi in the pulmonary arteries. Sections of the tumor from the auricle revealed large areas of necrosis and hemorrhage interspersed among masses of heterogeneously arranged spindle-shaped cells. In some areas the intact cells were arranged in perivascular fashion. In some areas the appearance suggested new formed granulation tissue with capillary proliferation, while in other areas the tissue appeared neoplastic in nature.

Case 2. H. L. C., a 26 year old white male, was admitted to the George Washington University Hospital on November 8, 1937, as a patient of Drs. Charles W.

Hyde and Ross Morris. Four months before admission the patient had noticed a slightly increasing general weakness to which he paid little attention. Two months before admission he developed what was believed to be a typical case of influenza characterized by malaise, generalized weakness and cough. After five days of rest in bed he attempted to return to work, but was unable to continue working because of weakness. Examination at that time showed an increased heart rate, and roentgen-ray examination of the chest showed cardiac enlargement. Following bed rest again, he lost ground rapidly and died on November 14, 1937.

Physical examination at the time of admission to the hospital revealed generalized glandular enlargement, cardiac enlargement and no murmurs. The liver was enlarged three fingers'-breadth below the costal margin. This enlargement increased to five or six fingers'-breadth at the time of death. Temperature ranged during his stay in the hospital from 96° F., to a maximum of 101° F. Pulse rate varied from 100 to 110 and respiratory rate remained around 22. Blood pressure was 115 systolic and 80 diastolic. Erythrocyte count on admission was 3.9 millions, hemoglobin was 70 per cent and leukocyte count was 5,100. At autopsy the body was that of a well developed and well nourished white male. Upon opening the peritoneal cavity the liver was found to extend from five to six fingers'-breadth below the costal margin. Two thousand c.c. of bile-tinged fluid were present. Numerous small hemorrhagic spots were noted throughout the omentum. These nodules ranged in color from light to dark brown and give a granular sensation upon palpation. The abdominal organs showed evidences of chronic passive congestion. The spleen weighed 95 grams and upon section whitish nodules on the surface were seen to extend several millimeters into the parenchyma. The right kidney contained a hemorrhagic nodule 1 cm. in diameter. On section the mass appeared to be a fairly recent infarct. Petechial spots were scattered irregularly over the surface of the kidney. The left kidney likewise showed petechial spots and several infarcts. The liver weighed 2070 grams and its capsule was thickened somewhat. In the center of the right lobe near its lower quadrant there was a nodular area about 1 cm. in diameter, which was redder in color than the surrounding liver parenchyma, but which was separated from it by a white zone. Several similar nodules ranging in diameter from 0.5 to 2 cm. were found throughout the liver. The gall-bladder was normal. The right pleural cavity contained 2000 c.c. of bloody fluid. Numerous areas, hemorrhagic in appearance were noted throughout the right pleural cavity. Similar areas of hemorrhagic extravasation were seen on the pleural surface of the right lung, which also showed on cut section infarcts and areas of atelectasis. The right lung was densely adherent to the mediastinal structures and pericardium by hemorrhagic nodular masses which were scattered rather diffusely in this area. The left pleural cavity contained 100 c.c. of clear straw-colored fluid. Changes in the left lung were similar to, but less obvious than those in the right lung.

The pericardium was firmly adherent to the heart which latter showed marked enlargement. The pericardium was markedly thickened, but could be removed with difficulty, revealing a red hemorrhagic surface with an enormous amount of fibrous connective tissue. The mediastinal lymph nodes were adherent to this fibrous hemorrhagic mass. On transverse section the myocardium was hemorrhagic and mottled and was involved by the hemorrhagic neoplastic tissue. A large nodule of the neoplastic tissue extended into the left auricle. The right auricle was almost completely obliterated by a hemorrhagic neoplastic mass. At the apex of the right ventricle was a smaller mass of neoplastic tissue. The left auricle showed no abnormalities. The left ventricular wall was markedly thickened. In the region of the apex the hemorrhagic neoplastic tissue invaded the myocardium of the left ventricle (figure 2).

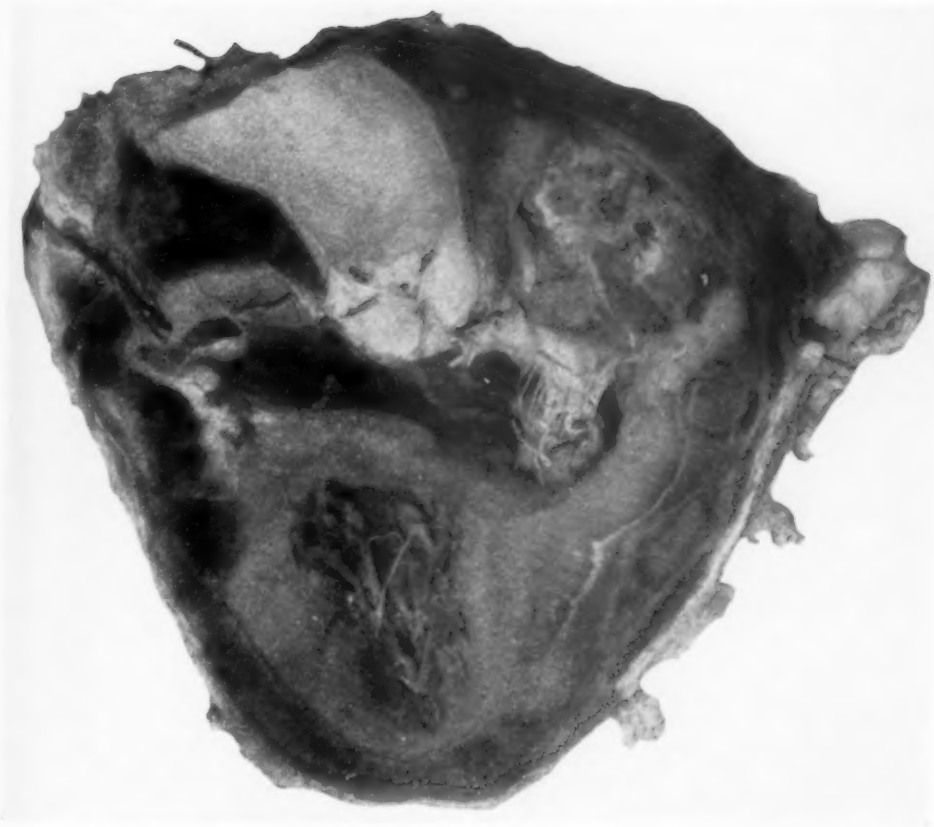

FIG. 2. Heart with adherent pericardium and tumor in right auricle, second case.

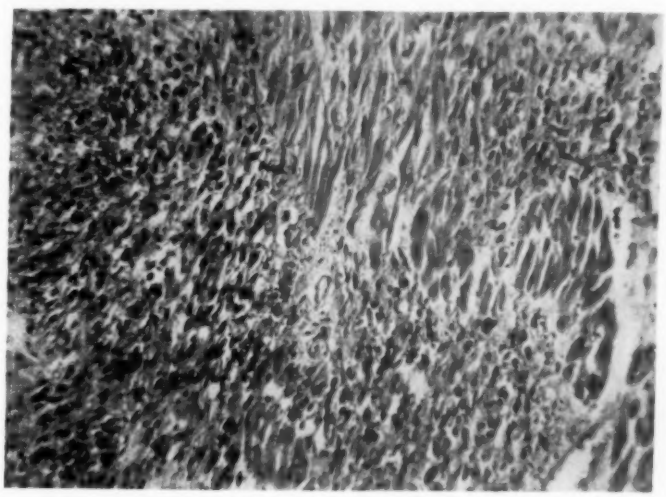

FIG. 3. Section showing invasion of myocardium by tumor, second case.

Upon microscopic examination the hemorrhagic neoplastic tissue presented a similar appearance regardless of the site from which it was obtained. The tissue was made up of spindle-shaped cells, varying in size, among which were many small blood vessels and a considerable amount of hemorrhage (figure 3). Occasional portions of the tumor showed areas of necrosis and occasionally mitotic figures were seen.

Discussion

Clinical characteristics presented by both of the cases here reported were rather those of chronic or subacute respiratory infection than otherwise. Norton has emphasized this aspect of cardiac tumors in his report. In the first case here reported, during the period of several months prior to hospitalization the patient developed increasing weakness, marked cough particularly during the night, varying amounts of sputum which was occasionally blood-tinged, and profuse night sweats. As termination of the disease approached, the mild jaundice present some two months previously decreased in intensity but never entirely disappeared. The nocturnal dyspnea and orthopnea increased in severity, and upon several occasions the nocturnal cough was productive of blood. The second of these two cases was practically identical except that in the terminal stages the evidences of respiratory infection were the outstanding symptoms.

A characteristic physical sign in both of the present cases was the peculiar edematous appearance of the face and neck. Although the skin seemed of normal texture it had taken on a wax-like appearance and seemed stretched over an increased amount of subcutaneous tissue. The facial edema was not so characteristic in the early stages, but by the time the patient was admitted to the hospital its characteristics were unusual enough to call forth comments from all observers and to be a factor in considering similar types of involvement in the two cases. Cyanosis never was particularly marked, but remained definitely noticeable throughout the course of the illnesses. The physical signs upon examination of the heart revealed little abnormality. Rate and rhythm remained normal in both cases and the sounds showed little variation from normal.

In comparison with the above clinical course the syndrome associated with myxomata of the left auricle as discussed by Bordley seems only suggestively distinctive. The palpitation, dyspnea upon exertion, and weakness, recurring in the episodes with intervals of freedom, as in Bordley's cases, are symptoms common to many types of disturbance. In addition these are symptoms which occur towards the end of the clinical course.

As mentioned by Yater [8] the accumulation of bloody fluid in the pericardial sac is highly presumptive evidence of a tumor of the heart. We should like to qualify and amplify this statement as follows. In the presence of bloody pericardial fluid, separation of cellular and liquid fractions should be done immediately upon obtaining the fluid. A relatively small proportion of intact erythrocytes in comparison with xantho-chromic supernatant fluid thus is of marked diagnostic value in these cases. Little attention seems to have been paid to this most important characteristic of pericardial fluid in this type of case.

In the case where the tumor involves the right auricle obviously it is difficult, upon roentgen-ray examination, for the individual unfamiliar with cardiac appearances to diagnose the nature of the right auricular tumor. In the Cabot case the increase in size of the tumor in the right auricle was traced in repeated roentgen-ray examinations. Six months before the patient was admitted to

hospital roentgen-ray films had revealed only slight prominence of the right auricle. Upon admission to the hospital a sharp " bulge " seen in the region of the right auricle proved to be, at autopsy, the tumor in the right auricle.

Analysis of the remaining symptoms and physical signs which occurred in the present cases, in their relation to other cases reported in the literature, is as follows.

Upper Respiratory Tract Infection. Norton's case was diagnosed upon admission to hospital as bronchopneumonia accompanied by acute toxic myocarditis. The patient reported in the Cabot case developed cough associated with fever and pain in the chest seven months before admission to hospital. The two cases reported here were characterized during the major portion of their illnesses by symptoms of subacute upper respiratory infections. In retrospect, it is obvious that these symptoms had their origin in the atelectatic, congestive, thrombotic and infarctive changes occurring in the pulmonary tissues throughout the clinical course of the disease. Any one of these types of pulmonary involvement is liable to give rise to fever, cough or hemoptysis. When they occur in combinations, with one type of disturbance more prominent at one time and another type at another time, the reason why quiescent intervals and exacerbations occur at various times is obvious.

At the present time it seems impossible by roentgen-ray examination of the lungs to diagnose at an early stage the changes just described. However, there seems no reason why, with improvement in technical methods and increased correlative studies, it should not be possible to diagnose small infarcted and atelectatic areas in the lung tissue. This would be valuable diagnostic evidence in the early stages of the disease.

We wish to emphasize here, therefore, the fact that in cases of neoplasm involving the right auricle the symptoms of respiratory system involvement are probably the outstanding ones during the major portion of the illness. We feel that it is among the group of atypical, prolonged " upper respiratory " cases, with subsequent development into " cardiac " types of cases, that there is offered the greatest possibility for correct clinical diagnosis. In fact, the similarities in the two cases here reported were so striking that, except for the probabilities of two such cases occurring within a period of six weeks being so very remote, the diagnosis of Kaposi's disease involving the heart would have been entertained more seriously than was the case.

When heart block, particularly the complete type, occurs, as is emphasized by Yater, there is considerable likelihood of clinical diagnosis of cardiac involvement. In such cases, however, cardiac involvement ordinarily is secondary to a neoplastic process elsewhere so that lesions in the heart are the result of metastatic involvement. In this rather rare type of primary cardiac involvement the lesion is located near the conducting system and is not a tumor of the auricle.

Cases in which there is variation in the patient's condition and physical signs from the recumbent to sitting posture, or vice versa, also seem likely candidates for cardiac tumors usually of types other than those described herein. The classic type of case giving physical signs which vary with posture is the one of ball valve thrombus. If too much attention is paid to this criterion there is liable to be much confusion with this type of case. Cases with atypical signs of

valvular involvement may be cases of cardiac tumor, but rarely will they be of the type discussed in this paper.

Hemoptysis, the coughing up of small amounts of blood, when interpreted as the result of rupture of a small blood vessel by excess pressure, in the presence of cyanosis and pulmonary symptoms, should suggest the possibility of increased pressure in the pulmonary system. The epistaxes probably are explainable by rupture of a vessel wall from the increased pressure of chronic passive congestion.

Summary

Two cases of idiopathic hemorrhagic sarcoma (Kaposi's disease) involving the heart are reported and discussed, with particular emphasis upon the clinical aspects of the cases. The identical clinical courses of the two cases, when compared with similar cases in the literature, constitute a syndrome which may permit of clinical recognition. The outstanding characteristics of this syndrome are as follows. Onset clinically is that of an acute upper respiratory infection which becomes prolonged to the subacute type. Cough, malaise, weakness, night sweats, sputum (occasionally blood-tinged) and hemoptyses occur at one time or another. Edema of the face, at first transitory, later becomes a most characteristic feature. Cyanosis remains constant for the most part, but increases upon occasion. Temperature elevations reach a maximum of 100 or 101 degrees. Roentgen-ray examination repeated at proper intervals may show the tumor mass in the auricle, with or without accompanying pericardial fluid. The latter, if present, is separated by centrifuging into a sediment of erythrocytes overlain by clear xanthochromic fluid.

Note: I am indebted to Drs. Charles W. Hyde and Ross Morris for the opportunity of including their case as the second one in this report.

BIBLIOGRAPHY

1. Raw, N.: Primary tumour of right auricle of heart, rupture of inferior vena cava, Brit. Med. Jr., 1898, ii, 1335.
2. Norton, W. H.: Myxoma of the heart simulating bronchopneumonia, Am. Jr. Med. Sci., 1919, clviii, 689.
3. Cabot Case, Number 22491, New England Jr. Med., 1936, ccxv, 1082.
4. Clerc, A., and Colleagues: Un cas de tumeur myxoide siegeant dans l'oreillette droite, Arch. d. mal. du coeur, 1937, xxx, 361.
5. Binder, A.: Ein Fall von primarem Sarkom des Herzens, Verhandl. d. deutsch. path. Gesellsch., 1913, xvi, 417.
6. Ehrenberg, L.: Zwei Fälle von Tumor im Herzen; ein Beitrag zur Kenntnis der Pathologie und Symptomatologie der Herztumoren, Deutsch. Arch. f. klin. Med., 1911, ciii, 293.
7. Bordley, James III: Tumor of the heart: a clinical report. Paper presented before the Johns Hopkins Medical Association, February 25, 1938.
8. Yater, W. M.: Tumors of the heart and pericardium, Arch. Int. Med., 1931, xlviii, 627.

DEATH PRESUMABLY DUE TO THE USE OF THE SALT RESTRICTION TEST IN THE DIAGNOSIS OF ADDISON'S DISEASE *

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THE use of a low salt diet as a diagnostic test in doubtful cases of Addison's disease was suggested by Harrop and his coworkers [1] in 1933. Two to five days after beginning the restriction of sodium chloride signs of relapse and characteristic concomitant alterations in the blood occur. That the test is dangerous has been recognized. Cortical extract, as well as intravenous salt solution, must be immediately available in event of a serious crisis.

This communication reports a sudden death occurring in a patient with Addison's disease during the period of a salt restriction test. Another report of death, presumably due to the use of the salt restriction test, has been published by Lilienfeld.[2] Since sudden death is common in Addison's disease, Lilienfeld did not think that a direct relationship between the salt restriction and the patient's death could be proved. He pointed out, however, that the use of the salt-free diet must be considered as a hazardous procedure.

CASE REPORT

W. C., a 51 year old white male, was admitted to Cleveland City Hospital January 7, 1938. His chief complaint was weakness for the past six months. The patient had been in good health until June 1937, when he noticed that his legs were unstable and that he was unable to walk with ease. He tired easily, and finally lassitude became so extreme that he was forced to bed. He had had occasional spells of vomiting, and had noted difficulty in swallowing food and epigastric discomfort after meals.

Examination showed the patient to be normally developed but extremely emaciated and dehydrated. The skin showed no abnormal pigmentation, but there was slight pigmentation of the buccal mucosa. The blood pressure measured in millimeters of mercury never exceeded 85 systolic, and the diastolic value averaged 60. Otherwise physical examination was negative.

The number of erythrocytes and leukocytes and the value for hemoglobin were normal. Urinalysis was negative. The spinal fluid Wassermann test and the blood Kline test were negative. The value of the blood urea nitrogen was 40.6 mg. per 100 c.c. of blood, but this later dropped to 15.1 mg. The value of the blood sugar was 72, of the sodium chloride 429, and of the cholesterol 192 mg. per 100 c.c. of blood. The basal metabolic rate was minus 27 per cent.

Fluoroscopic and film studies of the chest showed the heart to be smaller than normal. Several gastrointestinal series showed no evidence of a pathological process.

Because the case was thought to be not altogether typical of Addison's disease, the patient was placed on a salt-free diet in order to precipitate a crisis and thus establish a definite diagnosis. At the end of the customary six-day period there was no change in the patient's condition, and it was decided to continue the test a few days more. On the seventh day the patient was more lethargic than usual and did not take his food well. The blood pressure at that time was 80 mm. Hg systolic and 60 diastolic. The following day the patient refused food, but otherwise his condition seemed

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From the Departments of Medicine and Pathology of Cleveland City Hospital and Western Reserve University School of Medicine.

unchanged. On the next day, February 17, 1938, the patient suddenly went into shock and died before any therapy could be administered.

Autopsy

The autopsy was performed 15 hours after death. The body was that of a well developed but markedly emaciated white male. The heart weighed 250 gm. and showed brown atrophy. There was generalized arteriosclerosis, remote encephalomalacia of the left basal ganglia and a remote infarct of the spleen. Arteriosclerosis was slight, and there was chronic pulmonary emphysema, passive hyperemia, and edema of the lungs. The adrenals were grossly similar. The right weighed 2.7 gm. and its dimensions were 4.6 by 2 by 0.4 cm. The left weighed 2.5 gm. and its dimensions were 4.5 by 1.7 by 0.6 cm. The shape was normal. On the cut surface, the cortical portion, or what was interpreted as such, had a yellowish-gray color. The intensity of the color varied in portions of the organ. The tissue was definitely firmer than usual. No evidence of postmortem autolysis was discovered. The medulla was carefully searched for, but no gross evidence of the presence of this tissue could be demonstrated. The adrenal arteries revealed some sclerosis, but there was no obstruction or thrombosis. The thyroid, pituitary, pineal, and parathyroid glands were removed for examination. They showed no gross abnormalities. The rest of the organs showed no changes of importance in connection with this case. The heart's blood culture taken at the time of the postmortem examination showed no growth.

Microscopic examination of the adrenals demonstrated the following condition. No medulla was present. Extending throughout the central portion of the gland there was a band of acellular connective tissue. The cortical cells did not show the usual regularity of architecture, but were present in scattered foci or nodules. Some of these nodules showed completely degenerated cortical cells in which only the shadows of the cellular structure could be seen. In other places the cells were still present, but they were swollen and showed small dense nuclei. There were other nodules which originally had been cortical in situation. These now consisted of cholesterol and calcium. A few giant cells of the foreign body type were present. There was no evidence of tuberculosis. The fat stain gave an intensely positive reaction. In the capsule of the gland there were many mononuclear cells filled with brownish-red granules which stained positively for iron. A few contained a yellow pigment which was negative for iron. The arteries showed slight sclerosis.

Microscopic examination of the other organs gave no additional information of importance. In particular, the sections of the glands of internal secretion showed no significant changes.

The diagnosis was: (1) cytotoxic contraction of the adrenals including both the medullary and cortical portions; (2) generalized arteriosclerosis; (3) brown atrophy of the heart; (4) emaciation; (5) encephalomalacia, remote.

Comment

A death, presumably caused by the use of the salt restriction test in the diagnosis of Addison's disease, increases the evidence that this test is not without danger.

BIBLIOGRAPHY

1. Harrop, G. A., Weinstein, A., Soffer, L. J., and Trescher, J. H.: The diagnosis and treatment of Addison's disease, Jr. Am. Med. Assoc., 1933, c, 1850.
2. Lilienfeld, A.: The use of the low salt diet in the diagnosis of Addison's disease, Jr. Am. Med. Assoc., 1938, cx, 804.

COBRA VENOM INEFFECTIVE IN TWO CASES*

By WINGATE M. JOHNSON, M.D., F.A.C.P., *Winston-Salem, North Carolina*

IN THE ANNALS OF INTERNAL MEDICINE for April 1938, Dr. David I. Macht presented an intriguing article on the use of cobra venom for the relief of persistent pain. The impression was left with this reader, at least, that cobra venom was usually so effective in relieving persistent pain that it could be substituted for opium derivatives, and that in doses at intervals of two to four days it would keep a patient as comfortable as would several doses a day of morphine.

Since the only way properly to evaluate a new, or newly discovered, drug clinically is for enough practitioners to use it and compare results, and since I have seen no comments on Dr. Macht's article, I am submitting briefly my experience with cobra venom in two cases.

CASE REPORTS

Case 1. A 15 year old white girl two years ago had her right leg amputated above the knee because of sarcoma. In spite of roentgen-ray treatments subsequent to the operation the growth metastasized to the spine, causing constant pain. At the time the cobra venom was begun, she was taking ⅛ grain of morphine three times a day. The venom was given according to directions, 0.5 c.c. hypodermically the first day, daily doses of 1.0 c.c. for three days, then on alternate days for two more weeks. In spite of the venom morphine had to be given in increasing doses and at more frequent intervals. The verdict of all who were in attendance on the case was that there was apparently no appreciable effect from the cobra venom.

Case 2. A very intelligent and coöperative white male, 54 years old, had been confined to bed for more than two years with severe coronary disease. In spite of bed rest he was having a number of anginal attacks daily. When the cobra venom was first begun he was rather enthusiastic about the relief he thought it afforded, but this enthusiasm soon began to wane. When the ninth dose was due I found that the neck of the ampoule was cracked, so took advantage of this opportunity to give him 1.0 c.c. of boiled water instead of the venom. On my next visit he reported that he had had the most comfortable period of any since the treatment was begun. I never told him of the deception, but agreed to his request that the twelfth dose be omitted, as he had decided that all the relief he thought he had obtained at first was mental.

Unfavorable results, as well as optimistic ones, should be made known. Certainly these two cases seemed "made to order" for treatment by cobra venom, but in both it proved absolutely useless, except for the brief period of psychic effect in the second case.

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ORTHOSTATIC HYPOTENSION: CASE REPORT MENTIONING EFFECTIVE TREATMENT WITH BENZEDRINE SULPHATE*

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The condition of orthostatic hypotension, according to a survey of contemporary medical literature, is rare. Since the recognition of this clinical entity in 1925 by Bradbury and Eggleston, who described three cases, probably not more than a total of 50 instances have been published to date. Andrus, in this connection, as recently as September 1937, stated that about 30 cases of this condition had been reported, and Baker, in March 1938, was able to find only 38 instances of this syndrome after a careful search of medical publications. Orthostatic hypotension, however, is probably more common than we suspect, as undoubtedly many cases are not recognized.

Case Report

W. B., a white female, 67 years of age, was referred to the hospital by her family physician on August 11, 1938, for diagnosis. Her complaints were dizziness and fainting.

The medical history revealed typhoid fever at the age of 12, several attacks of influenza during her later years, and a chronic cystitis during the preceding 5 years.

Her surgical and family histories were irrelevant.

The onset of the present disturbance was in June 1933, with a sudden attack of vertigo soon followed by loss of consciousness, during which she fell down and struck her head. Since then the patient had approximately 200 to 300 experiences of dizziness which were succeeded by syncope. Vertigo alone had occurred so often that she was unable to recall any exact number of attacks. The dizziness and fainting were always worse during the morning and she stated, in this connection, that she invariably felt stronger in the evening. The majority of these attacks took place in her home, but a few proved embarrassing by occurring in public places. She herself noticed that a change in position from the recumbent to either the sitting or standing postures would invariably make her dizzy and often cause her to faint. At this point it is interesting to mention that many of her attacks of syncope had taken place en route from her bed to the bathroom. Experience had taught her that a prone position in bed was the safest.

Examination. The patient was an elderly, obese white female, 67 years of age, who was observed lying quietly in bed in the recumbent position. No pain, dyspnea, or discomfort was noted.

The routine admission findings were: pulse, 72 beats per minute; temperature, 98° F. (oral); respirations, 18 per minute; and blood pressure, 124 mm. mercury systolic over 80 mm. diastolic in the recumbent position.

The skin was sallow and somewhat greasy and coarse on palpation. No eruptions or scars were seen.

The eyes presented the following abnormalities. The right pupil was normal, but the left pupil was miotic. Both pupils, however, were round and regular and both responded to light and accommodation normally. Enophthalmos of the left eyeball and a decrease in the left palpebral fissure were observed. Ptosis of the left upper lid was present, and the left upper lid was weaker than the right when elevation was attempted.

* Received for publication February 13, 1939.

Fundus examination revealed moderate thickening, beading, and tortuosity of the retinal arteries in both eyes. The optic discs were normal and there was no evidence of retinal hemorrhage either old or recent.

The external auditory canals and drums of both ears showed no abnormalities. Hearing, as determined by the watch test, was equal on both sides and showed no impairment.

The patient was edentulous. The tonsils, although atrophic, showed evidence of mild chronic inflammation. The throat was normal and the uvula showed no deviation. The thyroid gland was slightly enlarged.

The superficial lymph glands were not palpable.

The chest was normal on inspection, palpation, and percussion, but auscultation revealed the presence of a few transient dry crackling râles heard posteriorly over the left apex, left base, and over the lower left axilla. The breasts were normal.

The apex beat of the heart was neither visible nor palpable. On percussion the position of the left cardiac border (M. L. 12 cm.) indicated slight enlargement. The cardiac sounds were of fair quality and A_2 was louder than P_2. No murmurs and no arrhythmias were heard. The blood pressure was 124 mm. mercury systolic over 80 mm. diastolic in the recumbent position.

The abdomen was slightly distended and a tympanitic note was elicited by percussion. The striae of previous pregnancies were visible. No masses and no tenderness were discovered on palpation.

The legs and thighs contained many superficial varicose veins, a few of which were thrombosed.

The peripheral arteries—radial, brachial, and temporal—were thickened and slightly tortuous.

Cystocele and rectocele were found on vaginal inspection. Rectal examination was negative.

Neurological examination showed that the superficial and deep reflexes were normal with the exception of the Romberg sign, which was positive. On standing the patient complained of dizziness and a sensation of impending faintness, and would have collapsed had she not been permitted to lie down. Pain and temperature sensations were intact and there was no recollection of any tingling, numbness, or paresthesia affecting the extremities. The grip of both hands was strong and the muscles of the arms and legs revealed no weakness nor atrophy. The speech showed no abnormalities, but a coarse generalized involuntary tremor was observed.

The mentality was clear and memory for past events was fairly good. There was no disorientation in regard to time, place, or person.

The impressions gathered from the physical examination were: 1. Horner's syndrome—left; (2) moderate arteriosclerosis of the retinal arteries; (3) moderate arteriosclerosis of the peripheral arteries; (4) adentia of both jaws; (5) mild chronic tonsillitis; (6) superficial varicose veins of the lower extremities; (7) cystocele; and (8) rectocele.

Laboratory. Two urinalyses were done which were normal. The hemoglobin was 82 per cent (Sahli method—17.3 grams of Hb. equals 100 per cent); there were 4,080,000 red blood cells, and 7,300 white blood cells per cu. mm. The blood Kahn test was negative.

Diagnosis. The history in this case was of extreme importance because it furnished the diagnostic clues. The story of vertigo and syncope following a change from the recumbent to the sitting or standing positions was suggestive of orthostatic hypotension. Special blood pressure and pulse examinations, with particular reference to changes in the patient's posture, confirmed this diagnosis. These examinations are tabulated as follows:

TABLE I

Position	Time	Blood Pressure	Pulse	Symptoms
Recumbent	3.15 p.m.	110/76	80	
Recumbent	3.16 p.m.	106/74	80	
Sitting	3.16½ p.m.	68/50	80	
Sitting	3.17 p.m.	72/58	82	
Sitting	3.17½ p.m.	82/60	76	
Sitting	3.19 p.m.	82/62	86	
Sitting	3.21 p.m.	82/62	78	Dizzy
Sitting	3.46 p.m.	78/66	80	Very dizzy—felt faint
Supine for 50 min.	4.36 p. m.	106/74	74	Felt better
Sitting	4.37 p.m.	62/50	84	

TABLE II

Position	Time	Blood Pressure	Pulse	Symptoms
Recumbent	After 15 mins.	138/84	80	
Sitting	15 secs. later	78/52	88	
Standing	15 secs. later	60–50/?	*	Dizzy, weak—felt faint

* Unable to obtain pulse rate because of rapid development of dizziness, weakness, and a sensation of impending faintness.

TABLE III

Position	Time	Blood Pressure	Pulse	Symptoms
Recumbent	After 15 mins.	128/86	82	
Standing	20 secs. later	84/?	84	Dizzy, weak—almost fainted

The diagnosis of orthostatic hypotension is based, therefore, on the following facts: (1) a history of dizziness, and dizziness rapidly succeeded by syncope on assumption of the upright position; (2) immediate severe fall in the systolic blood pressure accompanied by a simultaneous, but usually smaller drop in the diastolic pressure; (3) the unusual stability of the pulse rate despite the marked blood pressure changes; (4) the development of dizziness, weakness, and fainting on sitting up or standing; and (5) the marked symptomatic relief and general improvement produced by benzedrine sulphate.

In regard to diagnosis in this case it is interesting to note that the patient had been hospitalized on four previous occasions because of vertigo and syncope, and in no instance had the correct diagnosis been discovered. The reasons for failure to arrive at an earlier diagnosis in this particular instance are undoubtedly as follows: first, she was uncoöperative in her attitude and refused to stay in the hospitals long enough to permit a careful study of her condition; and second, orthostatic hypotension is a new and rare syndrome and because of its unfamiliarity may easily escape clinical recognition.

Later Course. The patient was returned to the care of her referring physician, who was acquainted with the diagnosis, with the advice that she be placed on benzedrine sulphate therapy—one 10 mg. tablet three times a day. He informed me four and a half months after the patient's hospital discharge that she had shown remarkable symptomatic and clinical improvement under the benzedrine sulphate treatment. She is now ambulatory and able to do some of her housework in the morning. In addition, she has not been troubled with fainting, and has experienced only an occasional attack of vertigo since beginning this form of therapy.

Etiological Consideration of Orthostatic Hypotension

This syndrome is regarded essentially as an imbalance of the autonomic nervous system in which both the sympathetic and parasympathetic divisions are affected. Two prominent features which indicate involvement of the sympathetic division are: (1) a peculiar diminution of reflex splanchnic vasoconstriction, which normally stabilizes the changes in blood volume in the dependent portions of the body when the upright position is assumed; and (2) a deficiency or absence of normal sweating which may be either localized or generalized in extent. Disturbance of the parasympathetic division is recognized by the abnormal maintenance of a comparatively stable pulse rate despite marked blood pressure fluctuations when postural changes are made. This phenomenon is caused by a failure of the vagus nerve to respond normally to blood pressure variations.

Bradbury and Eggleston in 1925 stated that the pathology was localized in the myoneural junctions of the splanchnic vessels and that true paralysis occurred. Ghrist and Brown, in 1927, while agreeing with Bradbury and Eggleston on the myoneural junction as the site of the trouble, considered the disturbance one of hypotonia rather than paralysis, and suggested, in addition, that this condition might be secondary to some primary cause. A comprehensive explanation of the vascular changes occurring in postural hypotension was reported by Ellis and Haynes in 1936. These investigators concluded that the syndrome was featured by: (1) a loss of reflex vasoconstriction of the splanchnic arterioles upon assumption of the upright position; and (2) by a loss of the reflex increase in the pulse rate on sitting or standing. The symptoms of weakness, vertigo, and syncope are, therefore, better understood after realizing that the simultaneous occurrence of three factors, i.e., severe stasis of blood in the splanchnic area, slow pulse rate, and abnormally low blood pressure, leads to a rapid and marked cerebral anemia when the upright position is attempted.

Many instances of orthostatic hypotension are undoubtedly idiopathic. Recent reports indicate, however, that an increasing number are associated with various pathologic conditions affecting the central nervous system. Ellis and Haynes reported in 1936 that 10 of 17 successive cases of tabes dorsalis showed characteristic falls in systolic and diastolic blood pressures in the sitting and standing postures. Orthostatic hypotension was also described in two instances of myasthenia gravis by MacLean and Horton in 1937. Other pathological states of the central nervous system found in association with postural hypotension are traumatic hematomyelia, syringomyelia, and a peculiar patchy type of arteriosclerotic degeneration widely disseminated throughout the entire central nervous system. In addition, according to Brown, Craig, and Adson, in 1935, an "acquired" form of orthostatic hypotension has occurred in some of their hypertensive patients following anterior rhizotomy of the lower thoracic and lumbar spinal nerves. Due to the frequent association of postural hypotension with certain pathological and surgical conditions of the central nervous system the question arises: is this association merely a coincidence or are these disturbances of the central nervous system the basic causes of the hypotension.

Treatment

Vasoconstrictor drugs are the most efficient agents capable of affording symptomatic relief in postural hypotension. The drugs of choice in this group are ephedrine sulphate, benzedrine sulphate, and neosynephrine hydrochloride. These drugs act by elevating the blood pressure through a prolonged vasopressor effect on the splanchnic arterioles. In this way a sufficiently high systolic blood pressure can be maintained to insure the hypotensive individual a considerable amount of physical freedom in the upright position. Successful treatment of orthostatic hypotension by ephedrine was reported in one instance by Ghrist and Brown in 1928. Ephedrine was most beneficial in their case when given every hour in 25 mg. doses. This dosage was later reduced to two or three capsules of 50 mg. each a day, and their patient was able to manage very well on this decreased amount. Korns and Randall, in January 1937, were the first to describe the beneficial value of benzedrine sulphate in one case, and three months later Davis and Shumway-Davis confirmed this work and published an account of effective therapy with benzedrine sulphate in two cases of their own. Baker, in 1938, reported the fourth case of orthostatic hypotension which has been benefited by benzedrine sulphate administration. There are some instances of postural hypotension, however, which do not respond favorably to ephedrine, benzedrine, or combined ephedrine and benzedrine types of treatment. Capaccio and Donald, in 1938, described such an instance in which they were successful in securing symptomatic relief by the oral use of neosynephrine hydrochloride in daily doses of 150 mg., finally reduced to 60 mg. Neosynephrine is a synthetic drug which is very closely related to epinephrine, but differs from epinephrine in that its vasopressor action is greatly prolonged. Neosynephrine may ultimately replace ephedrine sulphate in the treatment of orthostatic hypotension since the use of neosynephrine apparently does not produce the unpleasant secondary effects of cardiac arrhythmia, palpitations, nervousness, giddiness, and insomnia, which frequently follow the administration of epinephrine or ephedrine.

Summary

1. A case of orthostatic hypotension occurring in a white woman 67 years of age has been described.

2. Symptomatic relief and general improvement occurred promptly in this patient following the oral administration of 10 mg. of benzedrine sulphate three times a day.

REFERENCES

1. Bradbury, S., and Eggleston, C.: Postural hypotension: a report of 3 cases, Am. Heart Jr., 1925, i, 73–86.
2. Andrus, E. C.: The significance of acute hypotension: its etiology and treatment, Med. Clin. North Am., 1937, xxi, 1513–1522.
3. Baker, T. W.: Recognition of orthostatic hypotension: report of case, Proc. Staff Meet. Mayo Clin., 1938, iii, 169–174.
4. Ellis, L. B., and Haynes, F. W.: Postural hypotension with particular reference to its occurrence in disease of the central nervous system, Arch. Int. Med., 1936, lviii, 773–798.
5. MacLean, A. R., and Horton, B. T.: Myasthenia gravis with postural hypotension. Part 1, Proc. Staff Meet. Mayo Clin., 1937, xii, 787–792.

6. Brown, G. E., Craig, McK., and Adson, A. A.: The treatment of severe essential hypertension: effects of surgical procedures applied to the sympathetic nervous system, Minnesota Med., 1935, xviii, 124.
7. Ghrist, D. G., and Brown, G. E.: Postural hypotension with syncope: its successful treatment with ephedrine, Am. Jr. Med. Sci., 1928, clxxv, 336.
8. Korns, H. M., and Randall, W. L.: Orthostatic hypotension treated with benzedrine, Am. Heart Jr., 1937, xiii, 114–118.
9. Davis, P. L., and Shumway-Davis, Margaret: Orthostatic hypotension: The treatment of two cases with benzedrine sulphate, Jr. Am. Med. Assoc., 1937, cviii, 1247–1249.
10. Capaccio, G. D., and Donald, C. J.: Orthostatic hypotension: report of a case treated with neosynephrine hydrochloride, Jr. Am. Med. Assoc., 1938, cx, 1180–1182.

PFEIFFER BACILLUS MENINGITIS; THE CURE OF A CASE WITH SULFAPYRIDINE *

By C. C. McLean, M.D., F.A.C.P., Arthur W. Woods, M.D., and H. H. Henderson, M.D., *Birmingham, Alabama*

Due to the fact that the results in this particular patient were so spectacular, and that the dosage of the drug given was somewhat larger than is generally recommended, it was thought that a report of this case might be of interest.

Case Report

L. H., colored male, 30 months of age, weight 32½ pounds, was admitted to Hillman Hospital at 9:45 p.m., February 4, 1939, with a history of fever, vomiting, and headache of five days' duration. Entrance examination revealed a rectal temperature of 102° F., positive Kernig and Brudzinski signs, increased tendon reflexes, and a stuporous mental condition. The spinal fluid was obtained under slightly increased pressure; it was cloudy, and the cell count was 3,050 (90 per cent neutrophiles). Many gram negative bacilli and a few questionable gram negative diplococci were seen on smear. The culture of this fluid was reported as having an abundant growth of Pfeiffer's bacilli. The white blood count was 24,500, neutrophiles 82 per cent.

On February 5, 1939, at 6:00 p.m. sulfapyridine therapy was started.

Table I

Dosage of Sulfapyridine †

Dosage	Interval	Time
0.25 gm.	3 hours	Feb. 5 to Feb. 7
0.5 gm.	3 hours	Feb. 7 to Feb. 8
0.75 gm.	3 hours	Feb. 8 to Feb. 10
0.5 gm.	6 hours	Feb. 10 to Feb. 17
0.5 gm.	12 hours	Feb. 17 to Feb. 20
0.5 gm.	24 hours	Feb. 20 to Feb. 23

† Dagenan, 2-Sulfanilyl Aminopyridine, MB-693 (Merck & Co.).

Table 1 shows dosage, interval and the time the drug was given. The patient was first given 0.25 gm. every three hours, the size of the dose gradually being

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increased up to the maximum, which was 0.75 gm. every three hours. At no time during the administration of the drug was there the slightest toxic effect noted.

FIG. 1. The temperature curve of a case of Pfeiffer meningitis treated with sulfapyridine.

Figure 1 shows the temperature curve of the patient. Within 24 hours from the time the drug was started the temperature showed a continuous drop, and within 36 hours the temperature reached normal limits. At no time after this during the 20 days stay in the Hospital did the rectal temperature go above 100 degrees.

TABLE II

Examinations of the Spinal Fluid

Date	Cell Count	Smear	Culture	Differential Cell Count
2/ 4/39	3,050	Many gram neg. bacilli	Pfeiffer bacilli	90% neutrophiles 10% lymphocytes
2/ 9/39	200	No organisms	No growth	90% neutrophiles 10% lymphocytes
2/13/39	30	No organisms	No growth	
2/20/39	31	No organisms	No growth	80% neutrophiles 20% lymphocytes

On February 9 a spinal puncture was done. The cell count was 200, and no organisms were found in either the smear or the culture. At this time the neck rigidity had subsided considerably and the Brudzinski sign was absent. From that day forward the clinical course was uneventful, being marked by gradual recovery.

TABLE III

Examinations of the Blood

Date	Hb.	R.B.C.	W.B.C.	Polys.	L. Lymphs.	S. Lymphs.	Remarks
2/ 5/39	62%	3,370,000	24,500	82%	1%	17%	Wassermann test neg. Blood culture: no growth
2/ 9/39	52%	3,120,000	22,450	79%	2%	19%	
2/11/39			17,400	32%	0	68%	
2/15/39	68%	3,530,000	9,600	56%	0	44%	

On February 13 a spinal puncture was done; the cell count was 30 and no organisms were found in the smear or in the culture. On February 15 the white blood count was 9,600, neutrophiles 56 per cent.

EDITORIAL

MEDICAL CARE IN HANDICAPPED RURAL AREAS

MEDICAL care, adequate for the standards of the period, could be given in rural areas 40 years ago by general practitioners, in the home and office with occasional transferral of a difficult problem to the city. Advancing standards led to the widespread construction of rural hospitals, at first in the larger towns and then in smaller communities. Specialization in medical practice also has spread, first to the smaller cities and then to the towns, especially in certain sections of the country. Organized programs of preventive medicine have been extended into the rural areas.

Medicine, both preventive and curative, is a rapidly advancing science. Full advantage of its benefits can be obtained in rural districts only if in addition to well trained and equipped general practitioners there are available adequate local hospital facilities, an active health program, feasible arrangements for consultation with specialists, and a system whereby certain patients can be transferred for study or treatment to larger medical centers. Fortunately, in many rural regions these conditions obtain. The level of medical care in the more prosperous country areas is steadily rising.

There are, however, rural areas in many parts of the United States in which the picture as to medical care is far less encouraging. It is to be expected that wilderness areas with widely scattered sparse populations will be backward in medical care, but it is to well populated areas that we refer. Poverty of the population and remoteness from a medical center are two factors which combine in many instances to bring about a stationary or even a falling level of medical care.

The level of medical care in such an area cannot be determined with any accuracy by available statistics on the number of physicians, hospital beds and public health clinic visits, etc., though these figures yield a certain amount of information. Such quantitative measures are, however, deceptive. A qualitative survey on the ground is much more instructive.

In a remote and impoverished area of the country the number of physicians may be found to be quite adequate, and is only rarely grossly inadequate unless the country is very sparsely settled. The reason appears to be that in the first decade of the century the annual output of physicians was very large and was composed predominantly of men trained only for general practice. Even the remote areas of low economic status were well supplied. With the coming of automobiles and better roads, increasing a physician's range, the survivors of that period still constitute numerically an adequate number of physicians. If one studies, however, the number of young men going into practice in such areas the impression is gained that from now on, unless this number increases, there will be a growing scarcity of physicians.

This older group of men who have practiced their profession at a distance from medical centers in a population of low economic level have not as a class been able to keep abreast of many important advances in medicine and have lacked facilities for the application of many new measures of which they did gain knowledge.

The hospitals in such areas, although serving a purpose, are often extremely inadequate as to the facilities they afford. Numerically they may be sufficient, but many are merely old residences converted to hospital purposes and lacking in proper laboratory, roentgenological, nursing and consultant services. Public support from local sources for the medical care of the indigent is apt to be scant in these areas and the number of medically indigent is large. Care of such cases is a heavy burden upon the physician's resources of time and strength and often of money, for he frequently supplies the medicines. The care he can thus give is often restricted to emergency care.

Of course the low level of medical care in the regions referred to is only one evidence of their economic, educational, and social backwardness. There is usually a definite lack of awareness in the average citizen living under these conditions of the advantages to be gained by better medical care and an apathy which discourages those who attempt to improve conditions.

As the number of physicians decreases in such an area it becomes evident to all, however, that efforts to replace them must be made, for no matter how ignorant of the standards of medicine a farm laborer, a fisherman or a woodsman may be he knows he needs a doctor's help for himself and his family in illness. There is a growing demand on the medical schools for practitioners for these less favored regions.

The young physician completing his interneship hears of the requests and perhaps investigates. He finds that there is a bare living to be made from paid practice. He learns that he will have to assume, especially as a younger man, a crushing load of free work. He has been trained to employ all the facilities of a hospital, but in the territory which needs him there is no hospital worthy of the name. His progress has been aided by constant commingling with men whose special knowledge is his for the asking, but in this remote area it will be only through reading that he can enlarge his knowledge; and there will probably be little time or energy left for reading. Finally he feels that if he spends as much as five years in such practice, while learning much from experience he will nevertheless have lost so many skills from disuse and failed to learn so many new ones that it will be hard ever to break away and compete with other physicians in a large town or city. To a man who has spent three or four years in college, four years in the medical school and at least a year in a hospital the practice of medicine in a remote and unprosperous rural area has little indeed to offer.

There have been many actual attempts at a solution of this problem and even more theoretical solutions offered. None will be proposed here but certain conditions which must be met may be outlined.

The physician must see a chance for a reasonable livelihood in the region in which he works. If he were assured of receiving an adequate recompense for the care of the indigent and of the medically indigent this requirement could be met.

The facilities for practicing the type of medicine he has been trained for and of further developing his abilities must be furnished him. The raising of the standards of county hospitals and the physician's participation in well run special clinics will go a long way towards this goal.

A means of keeping contact with the advances in medicine must be made available to the rural physician. There are many devices for this purpose but none perhaps is sounder than the principle employed in medical schools. There, participation of the student in a program for the care of the indigent under his medical instructors is the basis of clinical teaching. Regular consultation clinics under teaching specialists as a part of the program for medical care of indigents in the rural area would have the same practical instructional value.

The meeting of these basic requirements need not involve "socialized medicine" nor anything detrimental to the ideals of the medical profession. It does involve a determined and coöperative effort on the part of all those chiefly concerned in medical care—the lay public, the practicing medical profession, the health department, the welfare department and others. These must combine to obtain for such handicapped areas the financial help which is necessary to establish a better level of medical care and to devise the medical care program. Only if the medical profession takes an active part in such a coöperative effort is it likely to find embodied in such a program the sound principles of medical care which its experience has demonstrated to be essential.

M. C. P.

REVIEWS

Clinical Diabetes Mellitus and Hyperinsulinism. By RUSSELL M. WILDER, M.D., Ph.D., F.A.C.P. 459 pages; 24 × 16 cm. W. B. Saunders Co., Philadelphia. 1940. Price, $6.00.

The author, who for the past 25 years has devoted the major portion of his time to the subject of diabetes, here presents most detailed clinical considerations of this disease.

The theory of carbohydrate metabolism, physiology and pathology of diabetes are presented only briefly. Liberal use of footnotes, a practice rather rare in medical literature, has been employed. For this feature the author is to be complimented. In this way contributory material is added without disturbing the main idea or thought.

Throughout the entire monograph the author freely states his own personal experiences and conclusions but gives due recognition to other workers who possess differing ideas. At the end of each of the 26 chapters extensive and complete references are given, thus greatly increasing the value of the book for those most interested in the subject.

The chapters on infection, surgery in diabetes, pregnancy, diseases of the thyroid and heart disease complicating diabetes are most outstanding.

The author's ideas, especially in respect to the proper diabetic diet and the treatment of diabetic acidosis (coma), are somewhat open for discussion.

The last four chapters are devoted to a most complete and careful review of the subject of hyperinsulinism—"the clinical opposite of diabetes."

This monograph is a most valuable contribution to the interesting subject of diabetes and is unreservedly recommended to the student and practitioner of medicine.

J. S. E.

Modern Medical Therapy in General Practice. Edited by DAVID PRESWICK BARR. 3 volumes. 3781 pages; 18 × 26 cm. The Williams and Wilkins Company, Baltimore. 1940. Price, 3 volumes, $35.00.

This important addition to the literature on therapy has appeared at a fortunate time to meet a real need. The advances in therapy have been so rapid in recent years and have occurred in so many divisions of medical practice that a system written by a large group of men, each covering the field of his special interest, saves the practitioner a great deal of research into the journal literature.

The selection of authors appears to have been very fortunate and their coöperation with the Editor, for which he thanks them in his preface, must have been unusually prompt, for all the sections reviewed appear to have included the very latest material to the date of publication. This must mean that all their labors were brought to a conclusion within a period of relatively few months—really an extraordinary achievement and one which adds greatly to the value of these volumes.

The amount of space allocated to various subjects has been influenced, the Editor tells us, by the purpose of presenting in detail those therapeutic methods which are adapted to use in general medical practice and only in outline such subjects as radiation therapy or artificially induced fever. On the whole, the length of the work (3 volumes, 3560 pages) has made it possible to give adequate space for a fairly detailed discussion of therapy in medical conditions. Here and there it appears that the length of the articles is not always proportionate to their importance. Thirty-four pages are made to suffice for the treatment of pulmonary tuberculosis, whereas fifteen are required for thrombo-angiitis obliterans. Only seven pages are given to the important subject of blood transfusions, whereas dietotherapy is discussed for 178 pages.

The first chief division is that of general therapy, which contains adequate, though summary, subsections on the use of drugs, gases, vaccines and sera, organotherapy, parenteral fluid administration, transfusion, diet, physiotherapy, occupational therapy, climate, etc. The excellent and sane discussion of various modes of physiotherapy is valuable and the whole section is very readable. The section on drugs contains a great deal of valuable information as to their uses and contraindications in brief and clear form.

It is not possible to review in detail the sections on general diseases, infectious diseases, and diseases of the various systems of the body. The real value of such a system as well as its weak points can become evident only through a number of months of continuous use as a reference in connection with the daily problems of practice. In so using it for a briefer period on numerous occasions the reviewer has been impressed with the high level of the contributions it contains. Moreover there is a minimum of extraneous matter and an evident attempt to give succinct practical descriptions of the therapy advocated. In most articles there is a touch of authority acquired by extensive personal experience which inspires confidence. It will be a valuable work for all medical men—students, general practitioners, and internists—and should serve as a standard reference for many years. The highest level of modern medical therapy has nowhere been more adequately presented.

M. C. P.

Some Fundamental Aspects of the Cancer Problem. Edited by HENRY BALDWIN WARD. 248 pages; 27 × 19 cm. The Science Press, New York City. 1937. Price, $2.00 (paper); $2.50 (cloth).

This book is composed of 30 papers read before the Atlantic City meeting of the American Association for the Advancement of Science, December 29, 1936 to January 1, 1937. These papers are put into five groups as follows:

1. Heredity and constitutional factors.
2. Induction, stimulation and inhibition of tumorous growths.
3. Metabolism of cancer tissue.
4. Radiation.
5. General discussion of cancer problems.

The authors of these articles are world-renowned scientists who have done much original research in their various fields. Among them are Maud Slye, C. C. Little, Francis Carter Wood, G. Failla, Charles Geschickter, et al. In the brief space allotted to this review, one can not begin to cover the subjects treated. The book furnishes a wealth of material and should be on the shelves of every person interested in cancer. So many fundamentals of the cancer problem are considered that the book becomes a ready reference volume for the cancer worker.

G. E. W.

Beyond the Clinical Frontiers. By EDWARD A. STRECKER, M.D. 210 pages; 21 × 14 cm. W. W. Norton & Co., New York City. 1940. Price, $2.00.

This 200 page volume represents Dr. Strecker's Thomas W. Salmon Memorial Lectures. It is essentially an application of lessons learned from the study of individual psychiatric patients and the problems of mass psychology, and a discussion of what the principles of mental hygiene have to offer in dealing with the "crowd-mind."

Dr. Strecker begins by considering the development of psychoneurotic and psychotic conditions as a retreat from reality. He takes up various commonly used methods of evading the ordinary responsibilities of living, points out some of the

things which make such evasion necessary to individuals and then compares the technics thus shown by mental patients and to a lesser degree by "normal man" to similar technics shown by the "crowd-man," as he exists in mobs and emotionally motivated movements. He reminds us that it has been pointed out that "in a complicated world, men cannot have an accurate picture of reality and consequently they construct a picture of that world which pleases them and which influences their behavior." Actual conditions surrounding people are not so important and determining as their conception of these conditions. Lippmann has labeled this expurgated edition of reality the "stereotype."

Dr. Strecker outlines certain characteristic stereotypes of individuals. He believes that crowds have similar stereotypes and that they develop a crowd-consciousness which can be traced and studied in the same way as that of a person and which influences the behavior similarly. The unfortunate aspect of the crowd-man as he exists in his group, is that "every spiritual superiority may be lopped off to the common measure and every little ego-consciousness may be stretched to the stature of full manhood. A small mind in a huge body is scarcely helpful in furthering an intelligent facing of reality." The crowd-man has obvious inferiorities, among the chief ones being his mediocre capacities, his commonplaceness and the childish character of his behavior.

This gives some general idea of his feeling about the working and ungoverned violence completely uncontrolled by intelligence, but directed by emotion, which is likely to emerge in propaganda-directed groups. This has led our civilization and our cultures into serious predicaments which merit psychiatric study in order to get some perspective into the motivations of behavior.

The last third of the book represents such a study. "When the psychiatrist looks at crowd-mindedness, whether it be in the emotional debauch of this or that movement or in a violent mob or in a nation at war, he simply sees on a large scale that which often he has observed at close range in his patients." Dr. Strecker believes the solution of the problem lies in individual education, aiming toward making it easier for the individual to recognize reality as it is and in taking some steps toward fixing the focus of our present reality on less extroverted ends, thus making it more tolerable and relieving many of the existing pressures. We could wish that Dr. Strecker would be a little more direct.

The book is readable but somehow we get the impression that there is a point which is missed, which would have made it much more usable. It leaves nothing particularly helpful to the individual in meeting the world as it is, nor does it give him any definite suggestions as to anything he can do toward altering it. This criticism is probably unjust, in that it applies not only to this volume, but to much of the mental hygiene propaganda.

H. M. M.

COLLEGE NEWS NOTES

Gifts to the College Library

Acknowledgment is made of the receipt of the following reprints by members of the College:

Dr. William Wallace Alexander, F.A.C.P., Florence, Ala.—1 reprint;
Dr. C. Charles Burlingame, F.A.C.P., Hartford, Conn.—1 reprint;
Dr. Hervey M. Cleckley (Associate), Augusta, Ga.—3 reprints;
Dr. William E. Costolow, F.A.C.P., Los Angeles, Calif.—4 reprints;
Dr. Joseph F. Elward (Associate), Washington, D. C.—7 reprints;
Dr. Archie L. Gleason, F.A.C.P., Great Falls, Mont.—1 reprint;
Dr. Marion Douglas Hargrove, F.A.C.P., Shreveport, La.—1 reprint;
Dr. Howard L. Hull, F.A.C.P., Yakima, Wash.—1 reprint;
Dr. Abraham E. Jaffin, F.A.C.P., Jersey City, N. J.—3 reprints;
Dr. Bert F. Keltz, F.A.C.P., Oklahoma City, Okla.—1 reprint;
Dr. Lionel S. Luton, F.A.C.P., St. Louis, Mo.—3 reprints;
Dr. Frank B. Marsh (Associate), Salisbury, N. C.—2 reprints;
Major Horace P. Marvin, F.A.C.P. (MC), U. S. A.—1 reprint;
Dr. J. R. S. Mays (Associate), Baltimore, Md.—1 reprint;
Dr. William Gerry Morgan, M.A.C.P., Washington, D. C.—38 reprints;
Dr. Hubert M. Parker (Associate), Kansas City, Mo.—2 reprints;
Dr. Arthur J. Patek, F.A.C.P., Milwaukee, Wis.—1 reprint;
Dr. Albert E. Russell, F.A.C.P., New York, N. Y.—2 reprints;
Dr. Louis H. Sigler (Associate), Brooklyn, N. Y.—1 reprint;
Dr. Albert Soiland, F.A.C.P., Los Angeles, Calif.—4 reprints;
Dr. Abraham Trasoff (Associate), Philadelphia, Pa.—10 reprints;
Dr. Charles F. Warren (Associate), Brooklyn, N. Y.—1 reprint;
Dr. Samuel Arthur Weisman, F.A.C.P., Minneapolis, Min.—2 reprints;
Dr. Howard F. West, F.A.C.P., Los Angeles, Calif.—3 reprints.

American College of Physicians Coöperating with Surgeons General of the Public Services

President James D. Bruce, with the approval of the Executive Committee of the American College of Physicians, during June appointed a Preparedness Committee consisting of:

Dr. James E. Paullin, F.A.C.P., Atlanta, *Chairman*
Dr. Roger I. Lee, F.A.C.P., Boston
Dr. Edward L. Bortz, F.A.C.P., Philadelphia
Dr. Ernest E. Irons, F.A.C.P., Chicago

to coöperate with the Surgeons General of the Army, Navy and Public Health Service of the United States, and with the Preparedness Committee of the American Medical Association in making available the services of the College to these Government agencies. Dr. Paullin is also a member of the Committee on Medical Preparedness of the American Medical Association.

In response to informal requests from the Surgeons General of the Army and Navy, the National Research Council organized the Division of Medical Sciences, of which the Committee on Medicine is a part. The Committee of the American College of Physicians is allied with the Committee on Medicine, of which Dr. Russell Wilder, F.A.C.P., Rochester, is chairman.

The Committee on Medicine held an organized meeting at Washington, June 29, 1940, which was attended by:

Dr. Arthur L. Bloomfield, F.A.C.P., San Francisco
Dr. James D. Bruce, F.A.C.P., Ann Arbor
Dr. Roger I. Lee, F.A.C.P., Boston
Dr. Warfield T. Longcope, F.A.C.P., Baltimore
Dr. Hugh J. Morgan, F.A.C.P., Nashville
Dr. Walter W. Palmer, F.A.C.P., New York
Dr. James E. Paullin, F.A.C.P., Atlanta
Dr. O. H. Perry Pepper, F.A.C.P., Philadelphia

and Dr. Russell Wilder, F.A.C.P., Rochester, Chairman, members of the Committee; Dr. L. H. Weed, Chairman of the Division of the Medical Sciences; and by invitation, Surgeon General James C. Magee, F.A.C.P., U. S. Army; Brigadier General S. U. Marietta, F.A.C.P., U. S. Army; Colonel C. C. Hillman, F.A.C.P., U. S. Army; Lieutenant Colonel James S. Simmons, F.A.C.P., U. S. Army; Captain L. E. Griffis, U. S. Army; Commander C. S. Stephenson, U. S. Navy; and Commander John R. Poppen, F.A.C.P., U. S. Navy. The meeting was devoted to a discussion of problems in the solution of which this Committee will be called upon for assistance. It was proposed that an executive committee be set up, consisting of chairmen of main committees with representation from the Army, Navy and Public Health Service. To this executive committee may come recommendations from the Committee on Medicine and the other main committees. The following sub-committees were established:

Infectious Diseases
Dr. Francis G. Blake, F.A.C.P., *Chairman*
Dr. Rollo E. Dyer
Dr. Henry Helmholz
Dr. Chester S. Keefer, F.A.C.P.
Dr. Stuart Mudd
Dr. Thomas M. Rivers

Venereal Diseases
Dr. J. Earl Moore, *Chairman*
Dr. Edwin P. Alyea
Dr. Charles Walter Clarke, F.A.C.P.
Dr. Oscar F. Cox, Jr.
Dr. J. F. Mahoney
Dr. John H. Stokes

Tropical Medicine
Dr. W. A. Sawyer, *Chairman*
Dr. Mark F. Boyd
Dr. Edward H. Hume
Dr. Thomas T. Mackie, F.A.C.P.
Dr. Henry E. Meleney
Dr. Robert B. Watson, F.A.C.P.

Cardiovascular Diseases
Dr. Paul D. White, F.A.C.P., *Chairman*
(Personnel to be selected)

Tuberculosis
Dr. Esmond R. Long, *Chairman*
(Personnel to be selected)

Nutrition
Dr. Russell M. Wilder, F.A.C.P., *Chairman*
Dr. V. P. Sydenstricker, F.A.C.P.
Dr. Tom D. Spies, F.A.C.P.

Dr. Dwight L. Wilbur, F.A.C.P.
Dr. James S. McLester, F.A.C.P.
Dr. Norman Jolliffe, F.A.C.P.

Diseases of Metabolism
Dr. James H. Means, F.A.C.P., *Chairman*
(Personnel to be selected)

Therapeutics
Dr. O. H. Perry Pepper, F.A.C.P., *Chairman*
Dr. Hugh J. Morgan, F.A.C.P.
(Others to be selected)

Clinical Investigation
Dr. Eugene F. DuBois, F.A.C.P., *Chairman*
(Personnel to be selected)

It is understood that the American Medical Association, through its Committee on Medical Preparedness, will provide the Governmental Services with the listing of United States physicians, together with their various qualifications, fields of specialty, etc.

Schedule of Examinations by Certifying Boards

The following Boards have announced schedules of their examinations as follows: For further details and application forms communicate with the respective secretaries.

American Board of Internal Medicine: William S. Middleton, M.D., Secretary 1301 University Avenue Madison, Wis.	Written Examination, October 21, 1940. Oral Examination, Philadelphia, December, 1940. Written Examination, February 17, 1941. Oral Examination, Boston, April, 1941, in connection with meeting of the American College of Physicians. Oral Examination, Cleveland, June, 1941, in connection with meeting of the American Medical Association.
American Board of Dermatology and Syphilology: C. Guy Lane, M.D., Secretary 416 Marlboro Street Boston, Mass.	Written Examination, October 28, 1940. Oral Examination, Chicago, December 6–7, 1940. Applicants in Group B take both the written and oral examinations; applicants in Group A take the oral examination only.
American Board of Psychiatry and Neurology: Walter Freeman, M.D., Secretary 1028 Connecticut Ave., N. W. Washington, D. C.	New York City, December 18–19, 1940.
American Board of Radiology: B. R. Kirklin, M.D., Secretary 102 Second Ave., S. W. Rochester, Minn.	Boston, September 26–29, 1940. Cleveland, June, 1941, at meeting of American Medical Association.

Regional Meeting of Maryland Members

Fellows and Associates of the American College of Physicians residing in Maryland hold two local meetings each year. The spring meeting was held in connection with a dinner at The Maryland Club, Baltimore, on Saturday, May 18, 1940, with forty-two members present. Dr. Louis Krause, College Governor for Maryland, presided and opened the meeting. Dr. W. Halsey Barker (Associate), Secretary, read the minutes of the preceding meeting. The Maryland group, which they currently call the "Maryland Chapter," regularly elects a chairman and a secretary each year. Dr. Wetherbee Fort, F.A.C.P., was elected president for 1940–41, and Dr. R. Carmichael Tilghman (Associate), secretary. The main purpose of the spring meeting was to report the events of the Cleveland Session of the College. Dr. M. C. Pincoffs, F.A.C.P., opened the discussion by commenting on the papers on military medicine, which he considered opened a new field of medical work. Dr. Sydney R. Miller, F.A.C.P., discussed the requirements for admission to the College, emphasizing that Associates elected in the future shall be required to be certified by one of the national certifying boards before becoming eligible for advancement to Fellowship. The local chapter expressed regret at Dr. Miller's retirement from the Committee on Credentials after many years of valuable service.

Excellent accounts were given of the scientific and social programs of the Cleveland Session by many of the members who had attended the Meeting, chief among whom were Drs. Settle, Legge, Beck, Gundry, Acton, and Tenner. Out of the discussions came suggestions for improvement in clinics, panel discussions, and scientific papers. A suggestion was further made that improved amplifying service be used in the larger clinic rooms. Dr. Pincoffs was asked if it would be feasible to have a reporter record the discussions of the clinics with the object of publishing these in the Annals. The Editor stated that this procedure had been tried previously but had not proved satisfactory.

After Dr. Krause read excerpts from the chief banquet address of Mr. Grove Patterson, Editor of the *Toledo Blade*, the meeting adjourned.

Dr. Louis Faugères Bishop, Jr., F.A.C.P., New York City, was elected President of the American Therapeutic Society for the year 1940–41 at the 41st Annual Meeting of this Society in New York City, June 7–8, 1940.

At the expiration of his term as Governor of the American College of Chest Physicians for the State of Wisconsin, Dr. Andrew L. Banyai (Associate), Wauwatosa, was elected Regent of that College for District No. 9, at the recent annual meeting of the American College of Chest Physicians held in New York City. Dr. Banyai presented a paper at this meeting on "Newer Aspects of Pneumoperitoneum Treatment of Pulmonary Tuberculosis."

Before a joint meeting of the sections on Medicine and Gastroenterology of the New Jersey State Medical Society, held in Atlantic City, N. J., June 4, 1940, Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, presented a paper on "The Essentials in Digestion and Absorption in Deficiency Disease." He was also awarded first prize for an exhibit on Deficiency Disease.

Dr. Kelly also presented an exhibit on Deficiency Disease before the Scientific Section of the American Medical Association Convention in New York, N. Y., June 10–14.

Dr. John R. S. Mays (Associate) resigned May 16, 1940, from the staff of the Milledgeville (Georgia) State Hospital to become Senior Assistant Physician in Psychiatry at the Spring Grove State Hospital, Baltimore, Md.

Dr. Milton Samuel Sacks (Associate), Baltimore, has been appointed Associate in Medicine and Head of the Department of Clinical Pathology at the University of Maryland School of Medicine as of October 1, 1940.

Dr. W. Bernard Kinlaw, F.A.C.P., Elmira, N. Y., addressed the Chemung County Medical Society recently on "Discussion of Differential Diagnosis of Hypertension."

The Eighth Councilor District Meeting of the Medical Society of the State of Pennsylvania was held in Warren, Pa., June 5, 1940. At the morning session Dr. Walter F. Donaldson, F.A.C.P., Pittsburgh, Secretary of the Medical Society of the State of Pennsylvania, gave a talk entitled "On This Rock." The following members of the College presented papers during the afternoon scientific session:

Dr. Belford C. Blaine (Associate), Pottsville, Pa.—"Primer on the Simplified Treatment of Diabetes";

Dr. George Booth, F.A.C.P., Pittsburgh, Pa.—"Childhood Diabetes and Its Problems";

Dr. Frank A. Evans, F.A.C.P., Pittsburgh, Pa.—"Management of Diabetes and Its Emergencies."

Among those who participated in the recent postgraduate course in cardiovascular disease for medical officers of the Veterans Administration, given at Hines, Ill., were:

Dr. James G. Carr, F.A.C.P., Chicago—"Arteriosclerotic Heart Disease";
Dr. Andrew C. Ivy, F.A.C.P., Chicago—"Physiological Aspects of Hypertension."

Dr. Henry Field Smyth, F.A.C.P., Philadelphia, Assistant Professor of Industrial Hygiene at the University of Pennsylvania School of Medicine, recently received the second annual award of the Pennsylvania Public Health Association for outstanding achievements in public health.

Dr. James E. Paullin, F.A.C.P., Atlanta, Ga., addressed a recent meeting of the Columbia (South Carolina) Medical Society on "Congestive Heart Failure."

At a recent meeting of the Greenville County Medical Society, Greenville, S. C., Dr. Eugene M. Landis, F.A.C.P., University, Va., presented a paper on "Pathogenesis and Treatment of Edema," and Dr. Staige D. Blackford (Associate), University, Va., presented a paper on "Spontaneous Pneumothorax."

Recently, Dr. Edward C. Rosenow (Associate), addressed the Pierce County (Washington) Medical Society on Poliomyelitis. A short time ago Dr. Rosenow entered private practice in Pasadena, Calif.

Dr. Soma Weiss, F.A.C.P., Boston, was one of the faculty of the 24th annual graduate medical course held at the University of Washington, Seattle, July 15–19, 1940.

Dr. Paul F. Dickens, F.A.C.P., Washington, D. C., spoke on "Diagnosis and Treatment of the Anemias" at the 21st annual session of the Association of Former Interns of Freedmen's Hospital, Washington, D. C.

Lieutenant Colonel Edgar E. Hume, F.A.C.P., Washington, D. C., recently addressed the Innominate Society, Louisville, Ky., on "The Army Medical Library of Washington and Its Collection of Early Kentuckiana."

Under the presidency of Dr. Burton R. Corbus, F.A.C.P., Grand Rapids, Mich., the Upper Peninsula Medical Society held its annual meeting in Menominee, July 10–11. Among the speakers on the scientific program of this meeting was Dr. Elmer L. Sevringhaus, F.A.C.P., Madison, Wis., who spoke on "Treatment of the Menopause."

Dr. Thomas K. Lewis, F.A.C.P., Camden, N. J., was named president-elect and Dr. Ralph K. Hollinshed, F.A.C.P., Westville, N. J., was named second vice president of the Medical Society of New Jersey at the annual meeting in Atlantic City, June 4–6, 1940.

Dr. Hubert B. Haywood, F.A.C.P., Raleigh, N. C., was installed as president of the Medical Society of the State of North Carolina at its recent meeting in Pinehurst.

Dr. Noble Wiley Jones, F.A.C.P., Portland, Ore., spoken on "The Problem of Atherosclerosis and Atherosclerotic Heart Disease" at the recent annual meeting of the Southern Oregon Medical Society in Ashland.

Dr. Ernest P. McCullagh, F.A.C.P., Cleveland, conducted a clinic and spoke on "Clinical Values of Testicular Hormones" at the annual spring clinic of the Lycoming County Medical Society held in Williamsport, Pa.

Dr. Martha Tracy, F.A.C.P., Assistant Director of Public Health of Philadelphia and retiring Dean of the Woman's Medical College of Pennsylvania, was recently honored at a dinner. Dr. Tracy had been Dean of the Woman's Medical College of Pennsylvania since 1918, but, because of her appointment as Assistant Director of Public Health, retired at the end of the college year.

Dr. Francis D. Murphy, F.A.C.P., Milwaukee, Wis., spoke on "Use of Sulfanilamide and Allied Compounds in Clinical Medicine" at an all-day program of the Marquette University School of Medicine Alumni Association in Milwaukee.

Dr. Alexander E. Brown, F.A.C.P., Rochester, Minn., addressed a recent meeting of the Medical Society of Milwaukee County (Milwaukee, Wis.) on "Sulfapyridine and New Compounds."

Dr. William B. Castle, F.A.C.P., Boston, was elected president of the American Society for Clinical Investigation at its recent annual session. Dr. Eugene M. Landis, F.A.C.P., University, Va., is secretary of this Society.

Dr. D. M. Holt, F.A.C.P., Greensboro, N. C., Chairman of the Public Relations Committee of the North Carolina State Medical Society for the past year, was elected First Vice President of the North Carolina State Medical Society at the last annual meeting of the Society at Pinehurst, N. C. in June. He was also reëlected Chairman of the Public Relations Committee.

Among the guest speakers at the annual meeting of the Pacific Northwest Medical Association in Spokane, Wash., July 10–13, were:

Dr. Andrew B. Stockton (Associate), Assistant Clinical Professor of Medicine, Stanford University School of Medicine, San Francisco;

Dr. Anton J. Carlson, F.A.C.P., Frank P. Hixon Distinguished Service Professor of Physiology, Division of Biological Sciences, University of Chicago;

Dr. Fred H. Kruse, F.A.C.P., Clinical Professor of Medicine, University of California Medical School, San Francisco;

Dr. William Edward Chamberlain, F.A.C.P., Professor of Radiology and Roentgenology, Temple University School of Medicine, Philadelphia;

Dr. Harold E. Robertson, F.A.C.P., Pathologist at the Mayo Clinic, Rochester, Minn.

Dr. Stuart Pritchard, F.A.C.P., Battle Creek, Mich., recently received the honorary degree of doctor of science from the University of Michigan, Ann Arbor, for "distinguished and outstanding contributions to the field of medicine and public health."

The speakers at the 73rd annual meeting of the Mississippi State Medical Association, held in Jackson, included the following:

Dr. Douglas D. Baugh, F.A.C.P., Columbus, Miss.—"Intercepting Cancer in the Female Reproductive Organs";

Dr. Robert Lyle Motley, F.A.C.P., Memphis, Tenn.—"Some Points in the Diagnosis and Treatment of Indigestion";

Dr. John G. Archer, F.A.C.P., Greenville, Miss.—"Some Observations of Bundle Branch Block";

Dr. Rudolph H. Kampmeier, F.A.C.P., Nashville, Tenn.—"Benign Tertiary Manifestations of Syphilis Presenting Difficulties in Diagnosis."

At the 58th annual meeting of the New Mexico Medical Society Dr. Carl Mulky, F.A.C.P., Albuquerque, was named president-elect.

Dr. Walter Reece Berryhill, F.A.C.P., has been named acting dean of the University of North Carolina School of Medicine, Chapel Hill, following the resignation of Dr. William deB. MacNider, F.A.C.P. Dr. MacNider, who has been dean of the School of Medicine since 1937, resigned to continue his research activities as Kenan professor of pharmacology.

Dr. Homer E. Prince, F.A.C.P., Houston, was elected president of the Texas Allergy Association at its recent annual meeting.

Dr. Milford O. Rouse, F.A.C.P., Dallas, was elected president of the Texas Society of Gastroenterologists and Proctologists at their third annual meeting held recently.

Dr. Paul Dudley White, F.A.C.P., Boston, delivered the oration on medicine at a joint meeting of the Medical Society of Virginia and the West Virginia State Medical Association, which was held at White Sulphur Springs, July 29–31. Dr. Walter C. Alvarez, F.A.C.P., Rochester, Minn., spoke on "The Patient Who Is Always Complaining" at this meeting.

Dr. Oscar G. Costa-Mandry, F.A.C.P., San Juan, P. R., has been made an honorary member of the Society of Physicians and Surgeons of Costa Rica. Dr. Costa-Mandry is now president of the Puerto Rico Medical Association.

Dr. Cesar Dominguez (Associate), Humacao, P. R., was recently reappointed a member of the Board of Medical Examiners of Puerto Rico.

At the recent annual meeting of the Arizona State Medical Association, Dr. William Paul Holbrook, F.A.C.P., Tucson, was chosen president-elect. Dr. Leslie R. Kober (Associate), Phoenix, is vice president and Dr. William Warner Watkins, F.A.C.P., Phoenix, is secretary of this association.

Dr. Francis Marion Pottenger, F.A.C.P., Monrovia, Calif., has been appointed a member of the state board of health.

Dr. Robert Lomax Wells, F.A.C.P., was recently elected one of the vice presidents of the Medical Society of the District of Columbia.

In May Dr. James B. Herrick, M.A.C.P., Chicago, was presented with the "Gold Headed Cane" by the University of California Medical School (San Francisco). Dr. Herrick received this award for his accomplishments in the practice of medicine, in teaching, and in investigation. In June he was awarded the honorary degree of doctor of science at the convocation of Northwestern University.

New York University College of Medicine, on June 5, awarded the honorary degree of doctor of public health to Dr. Nathan B. Van Etten, F.A.C.P., New York, N. Y.

Dr. Henry K. Mohler, F.A.C.P., Philadelphia, recently received an honorary degree from Juniata College (Huntingdon, Pa.).

The Medical Fellowship Board of the National Research Council, Washington, D. C., recently renewed the fellowship in medical science for study in the United States, during the year 1940–41, of Dr. Abe Ravin (Associate), Denver, Colo. Dr. Ravin will continue his study at Harvard University.

At the recent annual meeting of the American Society for the Study of Allergy, Dr. Robert L. Benson, F.A.C.P., Portland, Ore., took office as president; Dr. Milton B. Cohen, F.A.C.P., Cleveland, Ohio, was chosen president-elect, and Dr. Samuel M. Feinberg, F.A.C.P., Chicago, Ill., was elected vice president. Dr. James Harvey Black, F.A.C.P., Dallas, Tex., is secretary of this Society.

Dr. John H. Peck, F.A.C.P., Oakdale, Iowa, was installed as president and Dr. Benjamin Goldberg, F.A.C.P., Chicago, Ill., was named president-elect of the American College of Chest Physicians at their recent annual meeting in New York, N. Y. Dr. J. Winthrop Peabody, F.A.C.P., Washington, D. C., and Dr. Mathew Jay Flipse, F.A.C.P., Miami, Fla., were elected vice-presidents of this society.

Dr. Alan Brown, F.A.C.P., Toronto, Canada, was recently made a fellow of the Royal College of Physicians of London (honoris causa).

OBITUARIES

DR. JOHN GERALD FITZGERALD

Dr. John Gerald FitzGerald, F.A.C.P., Toronto, Canada, died June 20, 1940, at the age of fifty-seven.

Dr. FitzGerald received his M.B. degree in 1903 and his M.D. degree in 1920 from the University of Toronto Faculty of Medicine. In 1925 he received an honorary degree of LL.D. from Queen's University Faculty of Medicine. He undertook postgraduate study at Harvard Medical School, University of California Medical School and University of Toronto Faculty of Medicine. During the summer of 1910 he studied at the Pasteur Institute of Paris and Brussels, and during the summer of 1911 he studied pathology at Freiburg, Germany. In 1913 he was appointed Associate Professor of Hygiene at the University of Toronto Faculty of Medicine and conceived his plan for a school of hygiene in whose laboratories specific sera and vaccines of high quality and low price could be manufactured, which would serve Canada as a whole and make the school a national center for postgraduate work in public health.

During the World War he served as Major in command of a mobile laboratory in France and later became Assistant Adviser in Pathology to the 5th British Expeditionary Force.

In 1919 Dr. FitzGerald succeeded the late Dr. John Amyot as Professor of Hygiene. He was appointed Director of the Connaught Laboratories, which had been opened in 1917 following the generous gift of the late Sir Albert Gooderham. In 1923 he became a member of the National Health Division of the Rockefeller Foundation, which had provided a building and an endowment for the new School of Hygiene, fulfilling the foresighted ideas of the young scientist in 1913. During 1927 Dr. FitzGerald represented Canada at the Rabies Conference in Paris. In 1930 he was appointed to the Health Division of the League of Nations, on which he served six years and of which he was Vice President during 1933. In 1931 he was made Scientific Director of the National Health Division of the Rockefeller Foundation, and in 1932 he was appointed Dean of the University of Toronto Faculty of Medicine, holding this office for four years. In 1935 he was appointed a member of the Permanent Commission on Biological Standardization of the Health Organization of the League of Nations. In 1938 he became a member of a Subcommittee on Medical Research in the National Research Council of Canada.

Dr. FitzGerald was a Fellow of the Toronto Academy of Medicine, the Royal College of Physicians and Surgeons of Canada, the Canadian Public Health Association, the American Public Health Association, and the American College of Physicians since 1925. He was a member of the Canadian Medical Association, serving on the Executive Committee for many years, and a Fellow of the Royal Society of Canada, serving as a member of the

Council, and as President of Section V during 1932–33. He was Honorary Adviser in Public Health Administration of the Department of Health, Ontario, and Honorary Consultant of the Victorian Order of Nurses.

We have lost a man of rare gifts and rarer vision at an age at which rich fruits of a ripened judgment might have been the expected harvest for many years to come. The honors won by Dr. FitzGerald have brought unique lustre to Canadian Medicine. The memory of his gentle yet forceful personality will long live among his colleagues here and abroad.

J. Howard Holbrook, M.D., F.A.C.P.,
Governor, Province of Ontario

DR. OTIS BURGESS SPALDING

Lieutenant Commander Otis Burgess Spalding (Fellow, 1931), Medical Corps, United States Navy, was born November 14, 1875, in San Francisco, California, where he received his early education. He attended the University of California during the years 1893 and 1894 and graduated from Leland Stanford Jr. University Medical School (Cooper Medical School) in the class of 1898.

Following graduation, he served as ship's surgeon on the S. S. Maui. The years 1901 and 1902 were spent in postgraduate work in gynecology and obstetrics at Vienna, Berlin, and Dublin. He served as surgeon in the Women's Hospital, San Francisco, California, 1902–1903. From 1903 to 1917 he practiced his specialty of surgery, gynecology and obstetrics in his home city.

In 1917 he enrolled in the naval reserve and served as senior medical officer at the Naval Reserve Training Camp, San Pedro, California, and transferred to the regular service in November 1919. During his service in the Medical Corps of the Navy, he served in the x-ray departments of the Naval Hospital, Mare Island, California; the U. S. S. *Relief;* the Naval Hospital, Washington, D. C., and the Naval Hospital, San Diego, California. He was placed on the retired list of officers of the Navy on December 1, 1939, and died April 12, 1940.

Dr. Spalding was elected to Fellowship in the American College of Physicians in 1931. He was registered with the Council of Medical Education and Hospitals in 1933 as a fully qualified roentgenologist. In 1934 he was elected to Fellowship in the American College of Radiology.

The entire service record of Dr. Spalding is one of which his corps may well be proud. The possessor of a winning personality, sound judgment, and unimpeachable character, his was the type that adds lustre to his profession. The high order of his professional skill was evidenced particularly in his instruction of junior officers. He was exceptionally well informed and efficient as a roentgenologist and was well versed in physical

therapy. His work in deep therapy and his investigations of psittacosis and silicosis were of a high order.

Ross T. McIntire, M.D., F.A.C.P.,
Governor for U. S. Navy

DR. JOHN W. MOORE

Dr. John William Moore, prominent Charleston physician and Fellow of the College, died following a brief illness on July 20, 1940. He was 70 years of age.

Dr. Moore suffered a heart attack at his office on July 17 and died three days later. He was born at Lexington, Virginia, on November 6, 1869. He received his academic schooling at Washington and Lee University and was graduated in medicine from the University and Bellevue Hospital Medical College, New York City, in 1899. He practiced in Charleston from 1903 to 1917, and then served as a Captain in the Army Medical Corps during the World War. He later spent three years in China as a medical missionary. He then returned to Charleston in 1926 and engaged in private practice until his death.

Dr. Moore was an active business man in Kanawha County. At one time he was superintendent of the Charleston General Hospital, and was serving as superintendent of the Mountain State Hospital at the time of his death.

Dr. Moore married Miss Daisy Preston, of Lexington, Virginia, in 1908. She died in 1921. He later married Miss Laura Dyer Venable, who with one son, John Venable Moore, survives him.

Albert H. Hogue, M.D., F.A.C.P.,
Governor for West Virginia

DR. FREDERICK A. SPEIK

Dr. Frederick A. Speik, Fellow (1922), died in South Pasadena June 30, 1940. Dr. Speik was born in Stockton, California, in 1882. He was educated at the University of Chicago where he won all-American football honors in 1904 under the training of his friend, Amos Alonzo Stagg. His medical training was at Rush Medical College where he was graduated with a very high standing. He went to Cook County Hospital for his general medical service.

Dr. Speik began practice in Los Angeles in 1912. He held a professorship in clinical medicine and in the College of Physicians and Surgeons, then the Medical Department of the University of Southern California, and was one of the chiefs-of-staff of the Los Angeles General Hospital. During the war he was an official draft examiner. He was the author of numerous medical papers, and was a member of many professional and social organizations, among which were the Los Angeles County, California State and American Medical Associations, the Los Angeles Clinical and Pathologic

Society, and the American College of Physicians. He was a member of the staff of the Collis P. Huntington Memorial Hospital of Pasadena. He belonged to the Oneonta Club, the Annandale Country and other Southland clubs. He was a member of St. James Episcopal Church of South Pasadena.

Dr. Speik had a large and very active medical practice, and was widely known both in professional and civic circles. His large circle of friends and acquaintances join with his family in their sorrow for the loss of a good physician, husband and father.

EGERTON L. CRISPIN, M.D., F.A.C.P., Regent.

DR. ALBERT W. LEWIS, JR.

Dr. Albert W. Lewis, Jr., Atlanta, Ga., thirty-nine years of age, died May 13, 1940, after an illness of several months. Dr. Lewis was a native of Tennessee and graduated from the University of Tennessee College of Medicine in 1932. He was well known and liked in Atlanta where he was on the staffs of Grady Hospital and Piedmont Hospital. He was also Assistant in Medicine and Assistant in Pharmacology at the Emory University School of Medicine. He was a member of the Fulton County Medical Society, Georgia Medical Association, Southern Medical Association and an Associate of the American College of Physicians.

GLENVILLE GIDDINGS, M.D., F.A.C.P.,
College Governor for Georgia

DR. HARRIS HOWARD HAMLIN

Dr. Harris Howard Hamlin (Associate), Seattle, Wash., died suddenly March 19, 1940, of coronary occlusion. Dr. Hamlin had been disabled since a previous coronary attack in February, 1939, this being the second.

Dr. Hamlin was born in Seattle, September 11, 1896. He was graduated with the degree of Bachelor of Arts from Stanford University in 1922 and with the degree of Doctor of Medicine from the University of Kansas School of Medicine in 1929. He served his internship at the Montreal General Hospital, followed by a residency at the Boston City Hospital from 1930 to 1932.

He began practice in Internal Medicine in Seattle in 1932, and became an Associate of the American College of Physicians in 1938. He was a member of the King County Medical Society, Washington State Medical Association, Fellow of the American Medical Association and also was a member of the Seattle Academy of Internal Medicine. He was a member of the Visiting Staff of the King County Hospital from 1932 until his death.

Dr. Hamlin was high in the personal and professional esteem of those who knew him. The profession and the College have suffered a real loss in his premature death.

C. E. WATTS, M.D., F.A.C.P.,
Governor for Washington

MINUTES OF THE BOARD OF GOVERNORS

CLEVELAND, OHIO

APRIL 1, 1940

The first meeting of the Board of Governors, held in connection with the Twenty-fourth Annual Session of the American College of Physicians, occurred on April 1, 1940, at the Cleveland Public Auditorium, Cleveland, Ohio, 5:10 p.m., with Dr. Charles H. Cocke, Chairman of the Board, presiding, and Mr. E. R. Loveland, Executive Secretary, acting as Secretary of the meeting.

The following Governors, or their Alternates, were present: Dr. Fred W. Wilkerson, Dr. Fred G. Holmes, Dr. Lewis B. Flinn, Dr. Turner Z. Cason, Dr. Glenville Giddings, Dr. James G. Carr, Dr. C. W. Dowden, Dr. Eugene H. Drake, Dr. Henry M. Thomas, Jr., Dr. Robert O. Brown (representing Dr. LeRoy S. Peters), Dr. Charles F. Tenney, Dr. A. B. Brower, Dr. Ernest L. Boylen (representing Dr. T. Homer Coffen), Dr. M. D. Levy, Dr. Ramon M. Suarez, Dr. James F. Churchill, Dr. James J. Waring, Dr. Charles H. Turkington, Dr. Wallace M. Yater, Dr. Samuel E. Munson, Dr. Robert M. Moore, Dr. Thomas Tallman Holt, Dr. William B. Breed, Dr. Warren Thompson, Dr. Nelson G. Russell, Sr., Dr. Leander A. Riely, Dr. Edward L. Bortz, Dr. R. R. Snowden, Dr. John L. Calene, Dr. J. Owsley Manier, Dr. G. Gill Richards (representing Dr. Louis E. Viko), Dr. Harry L. Arnold, Dr. J. Howard Holbrook, Dr. Oliver C. Melson, Dr. Ernest H. Falconer, Dr. Fred M. Smith, Dr. Joseph E. Knighton, Dr. Henry R. Carstens, Dr. Edgar van Nuys Allen, Dr. Charles H. Cocke, Dr. Alexander M. Burgess, Dr. Kenneth M. Lynch, Dr. Paul K. French, Dr. Walter B. Martin, Dr. Charles E. Watts, Dr. Albert H. Hoge, Dr. Robert D. Roach (representing Dr. Hugh A. Farris), Dr. Charles F. Moffatt, Comdr. Eben E. Smith (representing Rear Admiral Ross T. McIntire) and Dr. Thomas Parran.

The Secretary read abstracted Minutes of the preceding meetings of the Board of Governors, which were approved as read.

Chairman Cocke addressed the Board briefly, expressing his gratification with the large attendance and welcoming the Alternates to the meeting. He reported a communication from Governor G. W. F. Rembert, of Mississippi, expressing regrets at his inability to attend.

Chairman Cocke requested the Executive Secretary to read a telegram from Dr. Frank J. Sladen, Director of the Postgraduate Course, "Industry in Medicine," just completed at the Henry Ford Hospital, Detroit. Mr. Loveland read the telegram, and Chairman Cocke requested Governor Henry R. Carstens, of Michigan, to bear to Dr. Sladen, on behalf of the Board of Governors, its commendation for his excellent work in directing this Postgraduate Course.

Secretary Loveland distributed lists of candidates for Fellowship and Associateship who had been elected by the Board of Regents, so that each Governor would be informed from the beginning of the meeting as to new members elected from his territory. The list is not hereunder repeated, because it appears in the Minutes of the Board of Regents of March 31, 1940.

At the request of the Chairman, Mr. Loveland then distributed a list of the Associates who had been dropped for failure to qualify for Fellowship within the maximum five-year period, as prescribed by the By-Laws. Members of the Board were given an opportunity to ask questions about any particular cases.

At the request of the Chairman, Mr. Loveland also presented the list of members who were subject to being dropped for delinquency in dues of two or more years' standing. Each Governor had previously been advised of each delinquency, so that

any possible effort might be made to spare any deserving member. Governor Walter B. Martin, of Virginia, interceded for Dr. William A. Shepherd (Fellow), Richmond, who he reported had been ill and out of practice. Governor Martin was advised by Chairman Cocke to report the situation to Dr. James E. Paullin, Chairman of the Committee on Public Relations, with the recommendation that dues be remitted because of illness and retirement from practice.

Chairman Cocke made a summary report to the Board of Governors concerning happenings and activities in the College during the past year, including losses by death, new elections, two Masterships, plans for the publication of a College History, additions to the Life Membership Roster and attendance in and success of the 1940 Postgraduate Courses.

At this point, Chairman Cocke called upon Dr. Henry M. Thomas, Jr., Chairman of the Governors' Committee to Survey Postgraduate Courses, to make his report.

Dr. Henry M. Thomas, Jr.: "Mr. President and members of the Board of Governors: This is a rather difficult report to summarize, because it covers a great deal of work, accompanied by sending out questionnaires not only to those pursuing the Courses, but to individual members of the Board of Governors; including also reports obtained from each Governor from those in his territory who pursued the College Courses. A few things came out clearly from the reports. Every one who has taken the Courses is thoroughly enthusiastic about them and delighted that he took the Course and hopes to take more. For instance, one of our members is just back from the Postgraduate Course he took in Iowa City. This is the third year he has taken these Courses and he states they are getting better every year. It would be amiss to go into a long report to tell you of the minor differences which came out of all the reports we assembled. These differences had to do with the time of year for the Courses. We obtained no vote which would allow us to settle that question. We also had no sufficient preponderance of opinion that helped us settle the question of the length of the Courses. One member had asked that there be three kinds of courses given each year—one of one week's duration, one of ten days and one of two weeks, so that men may choose according to the amount of time available from their work. Other points in which there was some difference of opinion concerned whether we should have specific courses or general courses, and where they should be held. In general, it was the clear opinion that these courses should be available, if possible, to the members who are going to the meetings, that they should not be on a date that would interfere with the meetings, many wanted them just before or just after the meetings, whereas some wanted them in the autumn or at some other time. One man suggested that, like the clinics that are given in Vienna by the American Medical Association, there be a bulletin service put in the 'Annals of Internal Medicine' whereby courses might be available pretty much all year long and accredited teachers of the College be allowed to give a course any time they desired, and to have it announced to the members through the journal. The suggestions we obtained were very numerous. We took this matter up as a fact finding committee, rather than a committee to elaborate suggestions, and we turned our findings to the Regents' Committee on Postgraduate Education, of which Dr. Hugh J. Morgan is Chairman.

"I am glad we made this investigation, because I, for one, held a rather narrow-minded conception of the problem. It now is clear to me that this activity of the College is a much more important one than merely pulling ourselves up by our own boot straps, that this program has more to do than just with our own education, that it is a part of the College's activities in the large field of Postgraduate Education. It has been a magnificent success. If one were to try to criticize, the only possible way would be to say that the numbers who have availed themselves of these courses are something in the range of 7 per cent of the members of the College. There are, how-

ever, four or five times that number who ask about the courses each year and who may take courses in future years, when courses suit their particular needs and when conditions make it possible for them to attend.

"Our plan of investigation included a letter to every Governor, asking him to send a report from every man in his territory who had taken the Courses. Here again our report is limited to the men who have taken the courses and not to the 93 per cent of the members who have not taken the courses, so that our report does not express an opinion of the College, but merely an opinion of those members who have taken the courses. There were many helpful suggestions as to methods of giving these courses. Some letters were quite critical and some of them were amusing, but most of them were entirely commendatory.

"I, as Chairman of this Committee, had some experience in giving one of the Courses for the College at Johns Hopkins. To give a course of two weeks, or two courses as we did, is an undertaking which requires a great deal of effort on the part of the faculty. It was very strong in my mind that the College was asking Johns Hopkins, the University of Maryland, the University of Pennsylvania, Harvard University and other institutions to do this Postgraduate Education for them, and so I approached the problem with a different slant. I may say that not a single member of our Committee, besides myself, joined in this opinion, so that when I asked them about this phase of it, they all were enthusiastic about continuing the courses along the lines we had already started. I was not interested in changing the method, but I did wonder whether inside our College we couldn't do more about it, and if when we go to Baltimore we couldn't have our College members do the job, or do most of the difficult work, and whether we could not send important Officers of the College to consult with the heads of departments. That suggestion was forwarded to Dr. Morgan's Committee, as were also all of our reports and the letters from each member of our Committee.

"I have tried to give you a resumé of our work and of the type of information that came from it, and report the fact that we made no immediate suggestions, except to pass on our facts to the Regents' Committee. We were informed by Dr. Hugh J. Morgan that our survey had been very helpful, and that a good many of the things had been incorporated in this year's plans."

Dr. Fred M. Smith, Governor for Iowa, who had just completed the direction of one of the College Postgraduate Courses in Cardiology, was asked for a report by Chairman Cocke.

DR. SMITH: "Dr. Cocke and gentlemen: In our Postgraduate Course at Iowa City we had a very fine group of men, and it was with considerable regret we saw them leave. The success of a course of this sort depends on someone being on the job all the time to see that everything is carried out. Not only that, but I have a feeling that any success that we may have had was dependent to a large extent on the fact that these conferences were made very informal. We really tried to get acquainted with these doctors. We began our work in the morning, and followed that with a clinic. Dr. Edgar V. Allen, College Governor for Minnesota, was with us one day and we had him give a clinic that day. Immediately after luncheon there was a period for round table discussion. These men were very free in asking questions. This was encouraged by the informality of the luncheons. The round table discussions were particularly helpful, an opinion in which Dr. Allen readily concurred. They gave each man an opportunity to discuss questions that certainly weren't brought out in the clinic, or, for that matter, in the morning's proceedings. We felt very happy about their attitude, and we felt that they really honored us in coming, and these doctors came all the way from Oregon, California, Louisiana, Pennsylvania and other States."

Chairman Cocke opened the meeting for a discussion of Dr. Thomas' or Dr. Smith's report.

Dr. James J. Waring, Governor for Colorado, said that he had been among those who took the Course in "General Medicine" at the University of Michigan, and the group had authorized him to express unanimously for them their great appreciation of the Course which had been managed and designed by Dr. Cyrus C. Sturgis. The faculty of the Medical Department of the University of Michigan had really spared no effort in any way in giving to the registrants all the information on the side of medical science, as well as every attention socially.

Dr. C. W. Dowden, Governor for Kentucky, reported that he had received many inquiries from non-members of the College about admission to these courses. He inquired if it would not be necessary to limit the attendance to members of the College only. Dr. Dowden recommended that admission to the courses be restricted wholly to members of the College until it became evident that some vacancies would be available, which could be assigned to non-members, especially those preparing for membership in the College or for certification by the American Board.

Secretary Loveland explained that the registration is handled through the Executive Offices of the College. A formal registration form is required, and a matriculation card is issued to each registrant upon payment of the specified fees. Registration for the current courses had been restricted to members, with the exception of the course "Medicine in Industry," for which there was not adequate demand from members, with the result that non-members were admitted.

On motion by Dr. Oliver C. Melson, Governor for Arkansas, seconded by Dr. Fred M. Smith, Governor for Iowa, and carried, Dr. Thomas' report was accepted and filed.

Chairman Cocke reported upon the proceedings of the Board of Regents at its meeting on the previous day.

Dr. Turner Z. Cason, Governor for Florida, reported that there would be a regional meeting of the Florida members of the College in Tampa on April 29, and that a number of doctors from Cuba would be entertained. From this group, the College might appropriately wish to start a College membership in Cuba. Dr. Cason extended an invitation to the Executive Secretary, Mr. Loveland, and to the President-Elect, Dr. James D. Bruce, and to the Chairman of the Board of Governors, Dr. Cocke, to attend. The invitation was extended also to all members of the Board of Governors if opportunity to attend presented itself.

Adjournment.

Attest: E. R. Loveland
Executive Secretary

Cleveland, Ohio

April 3, 1940

The second meeting of the Board of Governors, in connection with the Twenty-fourth Annual Session, was held April 3, 1940, at the Cleveland Public Auditorium, Cleveland, Ohio, 12:30 o'clock, with Dr. Charles H. Cocke, Chairman, presiding, and Mr. E. R. Loveland acting as Secretary.

The following Governors, or their Alternates, were present: Dr. Fred W. Wilkerson, Dr. Fred G. Holmes, Dr. Lewis B. Flinn, Dr. Turner Z. Cason, Dr. Glenville Giddings, Dr. C. W. Dowden, Dr. Eugene H. Drake, Dr. Henry M. Thomas, Jr., Dr. Robert O. Brown (representing Dr. LeRoy S. Peters), Dr. Charles F. Tenney, Dr. A. B. Brower, Dr. Ernest L. Boylen (representing Dr. T. Homer Coffen), Dr.

M. D. Levy, Dr. Ramon M. Suarez, Dr. James F. Churchill, Dr. James J. Waring, Dr. Charles H. Turkington, Dr. Wallace M. Yater, Dr. Samuel E. Munson, Dr. Robert M. Moore, Dr. Thomas Tallman Holt, Dr. William B. Breed, Dr. Warren Thompson, Dr. Nelson G. Russell, Sr., Dr. Edward L. Bortz, Dr. John L. Calene, Dr. J. Owsley Manier, Dr. G. Gill Richards (representing Dr. Louis E. Viko), Dr. J. Howard Holbrook, Dr. Oliver C. Melson, Dr. Ernest H. Falconer, Dr. Fred M. Smith, Dr. Joseph E. Knighton, Dr. Henry R. Carstens, Dr. Edgar van Nuys Allen, Dr. A. Comingo Griffith, Dr. Charles H. Cocke, Dr. Leonard H. Fredricks (representing Dr. Julius O. Arnson), Dr. Alexander M. Burgess, Dr. Orlando B. Mayer (representing Dr. Kenneth M. Lynch), Dr. Walter B. Martin, Dr. Charles E. Watts, Dr. Albert H. Hoge, Dr. Robert D. Roach (representing Dr. Hugh A. Farris), Dr. Charles F. Moffatt and Comdr. Eben E. Smith (representing Rear Admiral Ross T. McIntire). President O. H. Perry Pepper and President-Elect James D. Bruce attended as guests.

Secretary Loveland gave a brief review of the Minutes of the preceding meeting, and offered to read the full transcript, which, however, was not called for.

Chairman Cocke introduced President Pepper, who addressed the Board as follows:

"The duties of the Committee on Postgraduate Education have grown enormously, just as the College's participation in postgraduate education has grown enormously. The duties of the Committee on Postgraduate Education seem to divide themselves pretty clearly into two parts. There was that part which had to do with the policy of the College, and that involved the representation on the Conference Committee, which combines, as you know, the Council on Medical Education and the American Board, which in itself is going to be no small task because that Committee is eventually going to have the duty of passing on the qualifications of hospitals as reported to them by their field investigators. Secondly, that Committee had all matters of policy brought up to it, and those might be considerable in any year and might not.

"Then on the other half of the main division were the details of the matters with regard to the pre-meeting courses, an activity of the College that has proved very valuable, not only to the members who have taken the course but to many of the gentlemen who have given the courses, who have admitted that they think they have learned more from them and their hospitals were more stimulated by them than even the men who attended them.

"Now, it seemed to me that it was impossible to ask one man to carry that load, as Dr. Hugh J. Morgan has done in the past year or so, and in searching for a solution, it seemed there was a very logical one, and that was to keep the policy in the hands of the same committee, if Dr. Morgan could be persuaded to continue, to keep those matters in the hands of the Regents, who have the power to expend funds, but to create a new committee which would interest itself in developing the pre-meeting courses to an even higher level than they at present are, and to correlate perhaps those pre-meeting courses in some way—this is still all undecided—with sectional meetings perhaps, or even develop new programs along that line.

"Now there we approached a part of this general matter which comes much closer to the Board of Governors and the individual Governors than it does to the smaller body of Regents, and so I ventured to suggest that the work of that committee be subdivided into two committees, one of them remaining a committee largely or altogether of Regents, although that is not necessary; the second committee largely but perhaps not necessarily (this is in the hands of Dr. Bruce, of course) a committee of Governors. That has struck a responsive note in the thoughts of the Regents, and this new committee was authorized at the meeting of the Board of Regents. It seems to me that it offers a solution of the difficulties of the situation and puts the

work of the pre-meeting courses where it can best be done and in the hands of those who are most interested.

"I may say that the work of arranging those pre-meeting courses is far greater than one would at first think. One has to select the topics, the place, the man, the man has to be persuaded, and the thing has to be organized. A great deal of that is carried on by your Executive Secretary, and the Executive Secretary in combination with the Chairman of the new committee will, I suppose, as usual, carry the brunt of it, although the Governors of the States in which the pre-meeting courses may be planned ought to coöperate to the fullest. That, as I understand, is the setup, and if Dr. Cocke and Dr. Bruce see faults in that statement or omissions, they can supplement it.

"Now, if I may speak briefly on one other subject, I have no criticism of the duties of the President throughout the year. They are a pleasure. However, if they continue to develop sectional meetings, as the American College of Surgeons has, we are going to run into a problem. As Dr. Bortz will tell you, Dr. George Muller, President of the American College of Surgeons, this last year found that his Presidency turned out to be pretty nearly a full-time job. In that College they have a permanent Chairman of the Board, who takes all the administrative work off the President, carries on with a continuance of knowledge and policy as Dr. Crile did for years, and now Dr. Irving Abel has replaced him. We have no such Chairman of the Board. I am not sure that I favor one, but unless the President is relieved of the program arranging and certainly the administrative duties, he can't take on as much of the sectional meetings as the President of the American College of Surgeons has.

"Now, maybe we ought not to have as many sectional meetings. Maybe we ought to have just as many and that ought to be the President's main job. He would be able to do it if that were his job. I am just presenting the problem, not prejudging it.

"I am very critical of the President's duties at the meeting. He talks a great deal too much. He has to under our present setup. I think it is very unfortunate.

"On the other hand, the Vice Presidents have no duties whatsoever. I would like to work out some scheme whereby the Vice Presidents would be brought more into the picture of the College. Possibly some of the Vice Presidents might be made use of in the sectional meetings as the official representatives of the College. They are fine men. They wouldn't be Vice Presidents if they were not. I think that some of the sectional meetings ought to invite the Vice Presidents, not every one of them the President.

"Second, I think somehow or other the Vice Presidents ought to do some of the talking and relieve the President. He has to make his speech of response on Monday. He has to preside at two meetings of the Board of Regents. He has to speak once or twice at the business meeting, at which he presides. He has to speak at the Banquet. He has to deliver a Presidential Address. I think there are seven speeches; I have forgotten two or three of them. Then, gentlemen, he is invited to a very delightful lunch and asked to speak again.

"Cancer of the larynx in our Presidents, Dr. Bruce, shows a very high incidence from chronic irritation, and I think that it is not only hard on him, but it is hard on the membership. I think they would much rather hear three less speeches from him and one more from each of the Vice Presidents. Thank you." (Applause.)

Chairman Cocke then introduced President-Elect James D. Bruce.

DR. BRUCE: "Mr. Chairman, Mr. President and gentlemen: There is nothing I can add to what Dr. Pepper has said. The delegation of more duties in Postgraduate Education to the Board of Governors I heartily approve, the utilization of all the

Officers of the College, related particularly to the Vice Presidents—there again I find a responsive cord. . . .

"I assure you you will find me collaborating very effectively and very heartily in the matters the President has introduced."

Chairman Cocke recognized at this point Dr. Alexander M. Burgess, Governor for Rhode Island.

DR. BURGESS: "I have a particular case to present. A man among my associates, who is one of the best qualified men, told me recently that he had just qualified for the American Board of Internal Medicine, and that he thought therefore it would not be worth his while to seek Fellowship in the American College of Physicians. He said that he felt certification by the Board was all he wanted, or needed, in his community, and that Fellowship in the College would cost a great deal too much."

Dr. Burgess said that this young man was sacrificing his time for his clinics, is not getting along very fast financially and finds the matter of qualifying for certification and Fellowship in the College beyond his convenient reach. Dr. Burgess expressed the fear that this same attitude might be taken by many good men and inquired whether any consideration would be given to the further reduction of fees.

Chairman Cocke asked for discussion of the question, and reported that he had not observed this situation in his part of the country, which is less densely populated, with fewer medical centers and where men do not have the same opportunities which encourage them to seek those opportunities and advantages which the College affords.

Dr. G. Gill Richards, as a representative of the American Board of Internal Medicine, announced that it is contemplated, within the rather near future, that fees for the examination may be somewhat reduced. The reduction cannot be made at the present time, because the Board is attempting an affiliation with sub-specialties, to be started next year, and the Board may have to charge a small additional fee to those men who take not only the regular examination for Internal Medicine, but who take a special examination in a sub-specialty. It may be necessary to charge an additional $10.00 fee to those men. Until the Board can find out just how many are coming up for sub-specialty examination and what expenses that will entail, no definite step can be taken. Dr. Richards further said that he thought it desirable to consider whether or not both the College and the American Board could not together reduce their fees.

Chairman Cocke assured the group that the whole subject was under consideration.

Chairman Cocke called upon the Secretary to present or announce invitations for the 1941 Session of the College, in order that a consensus of opinion might be obtained from the Board of Governors. It was revealed that formal invitations had come from Boston, Baltimore, Philadelphia, Kansas City, Chicago, San Francisco and other cities.

Dr. Cocke asked the representatives from these cities, if present, to make such remarks as they desire.

Dr. William B. Breed, Governor for Massachusetts, was first to extend an invitation to the College to consider Boston, the invitation being extended by the medical schools, the Governor of the State, the Mayor of the City, the Chamber of Commerce, the medical societies and other groups.

Dr. Henry M. Thomas, Jr., Governor for Maryland, on behalf of Baltimore, stated that he felt it was very near Baltimore's turn for another Session of the College and that the Baltimore members are very anxious to extend an invitation and welcome the College there.

Dr. Edward L. Bortz, Governor for Eastern Pennsylvania, spoke on behalf of Philadelphia and presented the written invitations from the medical schools, the Philadelphia County Medical Society, the Chamber of Commerce, and other agencies.

Dr. A. Comingo Griffith, Governor for Missouri, spoke on behalf of the invita-

tion from Kansas City. Dr. Griffith made a point of the fact that Kansas City had been inviting the College for years, and extended a whole-hearted welcome to the organization.

At this point, Dr. William B. Breed moved that the Board of Governors recommend to the Board of Regents that the College select Boston. The motion was seconded by Dr. Charles F. Tenney, Governor for Eastern New York, put to a vote and carried.

After the reading of some general announcements, the meeting adjourned.

Attest: E. R. LOVELAND,
Executive Secretary